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PLASTIC STUDIES IN ABNORMAL RENAL ARCHITECTURE

I. THE TWO ARCHITECTURAL UNITS IN CHRONIC BRIGHT'S DISEASE AND THEIR POSSIBLE FUNCTIONAL SIGNIFICANCE

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AND

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There are three ways in which the resultant of the processes that comprise a chronic disease can be considered. The first and oldest of these, that in which the picture is studied as a lesion of tissues, is of historical importance only, for the method of Bichat was soon superseded by the introduction of the microscope as an instrument of research and the consequent development of Virchow's concept of disease as a complex of cellular phenomena. The third method, which is derived chiefly from those systemic functional disturbances that demand the attention of the clinician, is to consider disease as a manifestation of organ derangement. A complete picture can therefore be obtained only by a combination of these two methods, and though, by a synthesis of particulars, there may logically follow from the detail of the cellular disturbances in an organ an understanding of disease as a manifestation of organ abnormality, the emphasis in such a procedure is from the first, and too often in the end remains, on the ultimate units involved, with a corresponding neglect of the total effects that have been produced by them.

It was this fact, no doubt, that in 1916 led Jores,[1] impressed in his studies of chronic disease of the liver, kidneys and blood vessels by the importance of changes affecting the organ *qua* organ, to suggest the word "metallaxis" as a general term to sum up and throw emphasis on alterations in the architecture of organs. A cirrhotic liver, as he showed, is not simply a liver in which connective tissue cells have developed and epithelial cells have degenerated or disappeared, but almost in a literal sense a new organ, the original tissues and architectural plan of which have been entirely replaced by a more or less complete *Umbau* (rebuilding).

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This work was done with the support of the Josiah Macy, Jr., Fund.

1. Jores, L.: Virchows Arch. f. path. Anat. **221**:14, 1916.

That all this is true of the kidney in the terminal stages of Bright's disease has been evident since the work of those who, from Weigert to Löhlein, established the details of the processes involved, and its significance, if not generally appreciated, has been strongly emphasized by Oertel.[2] We recently gave a summary of these points in the statement that the kidney in chronic Bright's disease is in the strict sense no longer a "kidney," so severely has metallaxis affected its constituent structures.[3] The importance of this fact in a proper understanding of the functional disturbances which lead to the clinical manifestations of the disease can hardly be overstated, for the unfortunate result is that it now seems unlikely that the functioning of the normal kidney, even if it were perfectly understood, could ever be transferred in toto or with simple additions or subtractions of quantitative matter to the diseased organ whose new structure suggests so strongly qualitative differences in activity.

As has been said, the details of the changes occurring in the cells, glomeruli, tubules and vessels have been accurately described; it is the "general elevation" of the new structure as a whole that is not clear. And this we believe to be due in part to a lack of studies in which the third dimension has been demonstrated as an objective datum rather than as a subjective projection in the mind of the observer. The great importance of such objectivity will be realized if one appreciates the sense of reality that the plastic models of Huber and Peter brought to the analogous problem of the architecture of the normal organ. And so it was our purpose in the present work to apply the method employed by these two investigators to the kidney in Bright's disease. The problem first considered was the variation in form, size and topography that occurs in the glomerulotubular unit and its adjacent vessels in the contracted kidney in terminal hemorrhagic Bright's disease (chronic glomerular nephritis). This was done by viewing the structural alterations in three-dimensional form as they were manifested by models of typical units. One showed an increase in size, the result of hypertrophy; the other, a decrease, the result of atrophy.

TECHNIC

The method used in the construction of the two models was the conventional Born wax plate procedure as modified by Peter.[4] The drawings of 5 micron sections from a perfect series were made at a magnification of 200 times on large sheets of paper. When a con-

2. Oertel, H.: The Anatomic Histological Processes of Bright's Disease, Philadelphia, W. B. Saunders Company, 1910.

3. Addis, T., and Oliver, J.: The Renal Lesion in Bright's Disease, New York, Paul B. Hoeber, Inc., 1931.

4. Peter, K.: Untersuchungen über Bau und Entwickelung der Niere, Jena, Gustav Fischer, 1909.

siderable number had been completed, the section showing the exit of the proximal convoluted tubule from the glomerulus was found, and from this definite point of departure the convolutions of the tubule were traced back and forth through the drawings. As each cross-section was identified it was given a number, and the number changed when the tubule changed its direction. As the work proceeded, more cross-sections were added to the drawings as needed, and the course of the complete proximal convolution from its origin to its terminal portion was thus eventually followed.

The identification of the distal convolution including the connecting tubule and the collecting tubule, offered a somewhat more difficult problem. No certain point of departure was available, since it is impossible to trace the tubule through Henle's loop, a distance of from 6 to 8 feet (about 2 to 3 meters) at our magnification and then back to the region of the glomerulus. Cross-sections of what appeared to be the corresponding distal convolutions were therefore chosen and followed through the drawings. The fifth attempt proved successful, as was shown by the inclusion of the selected tubule within the loops of the proximal convolutions.

This distal convoluted tubule was then followed downward into the broad ascending limb of Henle's loop and upward through the connecting tubule into the collecting tubule. Wax plates, 1 mm. in thickness, were next cut from the completely traced and numbered drawings, and these were carefully oriented and assembled in proper order. On completion of the assemblage a minimum amount of finishing was done with a hot iron and with a brush and hot wax to give the contours their natural surface. Great care was taken neither to increase nor to decrease diameters by these procedures, a danger that could be easily avoided by reference to the original dimensions in the drawings.

The difficulties encountered in the application of this method to the abnormal kidney as compared with those encountered in the reconstruction of the normal organ are considerable. They are due to the distortion of the already complex normal relations of one structure to the other that results from shrinkage of connective tissue scar and the increased tension where excessive hypertrophic growth has occurred.

MATERIAL

The kidneys selected for study were from a case of terminal hemorrhagic Bright's disease (chronic glomerular nephritis) in a series the clinical and pathologic manifestations of which have been previously described.[5] A summary of these observations is given here.

5. Addis and Oliver,[3] p. 238, case XV.

OBSERVATIONS IN A CASE OF HEMORRHAGIC BRIGHT'S DISEASE

The clinical diagnosis was hemorrhagic Bright's disease, in the active stage. The condition had been present for eleven years and under observation for the last six years. The etiologic background was streptococcic tonsillitis.

The initial stage passed without pronounced symptoms and was followed by a latent stage which lasted for seven years, broken only by three transient periods of activity resulting from infections. There was then a gradual transition to an active stage which continued until death. The terminal stage, though approached, never fully developed clinically.

Pathologic Observations.—The kidneys alone were obtained after death. They were normal in size, measuring 11.5 by 6 by 4 cm. The capsule was somewhat adherent, and when stripped left a finely granular, grayish-pink surface studded with small irregular yellowish points. No hemorrhages were visible. The cut surface showed a cortex of approximately normal width, opaque and grayish-yellow. The arteries were not thickened.

Microscopic Examination.—General: The cortex was somewhat reduced in thickness by the contraction of the new-formed inflammatory connective tissue that infiltrated it. The general picture of a patchy metallaxis was produced, islands of cortical tubules of normal or of increased size alternating with areas of dense fibrous scarring in which glomeruli were fibrosed and tubules collapsed (fig. 1).

Glomeruli: Every glomerulus examined in many sections was involved by the inflammatory process. Some were enlarged to about twice their normal size; the capillary tuft was infiltrated with leukocytes, including polymorphonuclears, and the capsular space was filled with a coagulated exudate of fibrin, leukocytes and endothelial cells. In others the same inflammatory lesions were found with accompanying organization of the exudate and fibrosis of the tuft. Still others had been transformed into solid masses of collagen in which no capillaries remained.

Tubules: The epithelium of the convoluted tubules and broad ascending limbs of Henle's loops showed widespread degenerative lesions. In some the lesions consisted of a simple granular degeneration; in others the epithelial cells were swollen and filled with large hyaline droplets. In scattered areas the cells were filled with fat droplets of irregular size. There was no frank necrosis of the epithelium in any of the tubules, but in many there was considerable desquamation of the lining cells. In such areas there was an irregular regeneration of the epithelium.

In the lumens of the convoluted tubules and occasionally in the limbs of Henle's loop were granular material and leukocytes, many of the latter of the polymorphonuclear type; more rarely red blood cells were found. In the straight tubules of the medulla were many casts of all sorts, hyaline, granular and epithelial. An occasional blood cast was found by careful search.

Interstitial Tissue: Throughout the cortex there was a diffuse and extensive proliferation of the interstitial tissue with an accompanying collapse and atrophy of the tubules. In this tissue there were large areas of heavy leukocytic infiltration; most of these cells were lymphocytes but a few were polymorphonuclear leukocytes.

Arteries: The larger arteries between the cortex and the medulla showed a moderate fibrous thickening of the intima. The change was not extreme in any of the vessels.

To summarize, the kidneys showed extensive involvement, the lesions consisting of the early and later stages of an extracapillary glomerulitis, all forms of epithelial degeneration and the presence of casts of all types. The proliferative

changes in the interstitial tissue of the cortex had destroyed a great part of the excretory tissue and profoundly altered the architecture of the kidney.

A block of tissue from a representative portion of the central part of the kidney was removed and embedded in paraffin. A complete and perfect series of sections, 5 microns in thickness, was then cut and stained with hematoxylin and

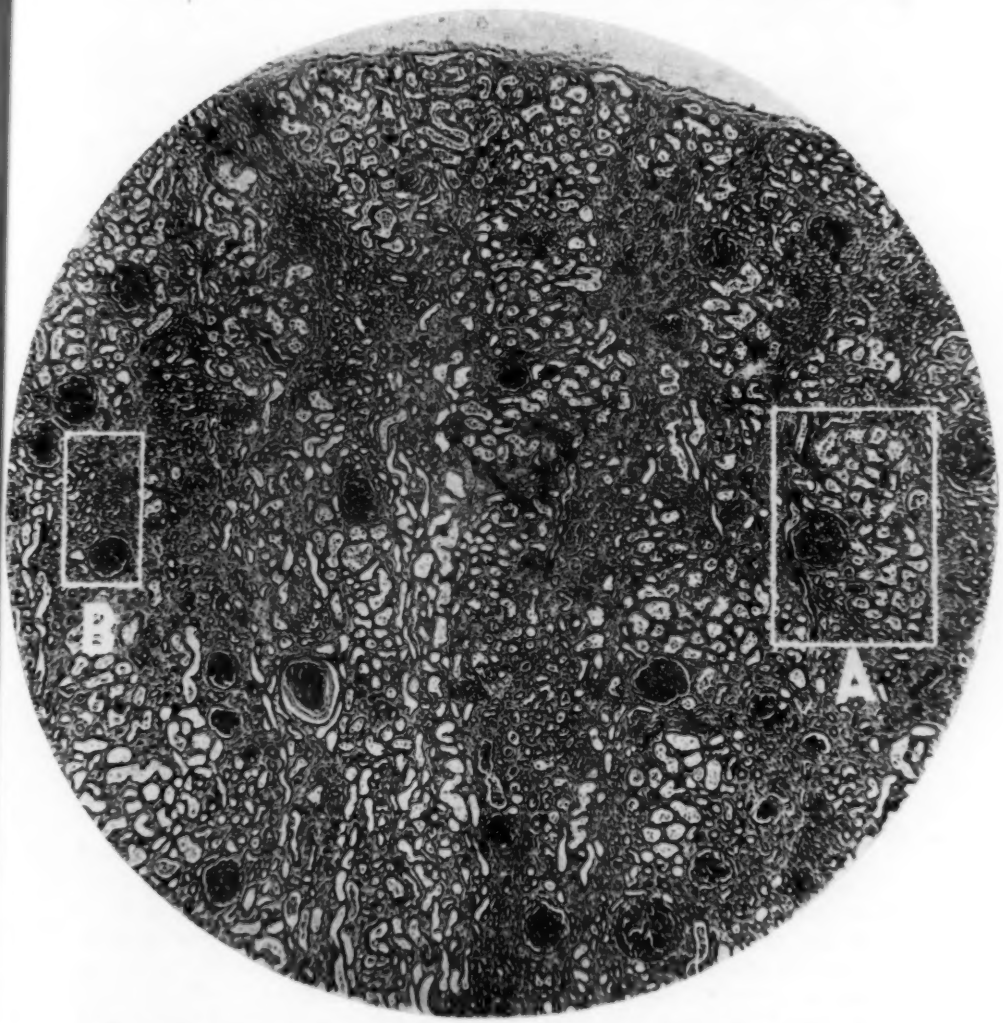

Fig. 1.—General view of cortex showing the patchy nature of the metallactic processes and the situation of the hypertrophic (*A*) and the atrophic (*B*) unit; × 28.

eosin. A mass of tissue from the surface of the organ and including the medulla was thus contained in the slides of the series.

A Hypertrophied Glomerulotubular Unit.—An island of cortical tissue near the middle of the series was selected that contained an enlarged glomerulus and

its surrounding convoluted tubules. The tubules, though not greatly dilated, were greatly increased in diameter. The enlargement of the structures in this group was as great as any that could be found in the section, and was therefore considered to represent the maximum effect of hypertrophy in the case under consideration. As seen in figure 1 *A* the unit lay in the upper third of the cortex, corresponding to one represented in figure 63 of plate A in Peter's monograph.[4] It is therefore an example of the "short loop" type of tubule.

A detailed description of the characteristics of the various structures in the unit is given as they appeared in the section that passed through its center (fig. 2).

Glomerulus: The glomerulus was definitely increased in size, but its section presented the undistorted normal round shape. The tuft was greatly enlarged, so much so that it completely filled and practically obliterated Bowman's space. There was extensive adhesion between the tuft and the capsule, so that the space was represented in section by occasional narrow slits which apparently did not open into each other. When the slitlike spaces were followed through the serial sections, however, they were found to form a communicating tortuous system of passages from one of which the proximal convoluted tubule arose.

The enlargement of the tuft was in part due to the development of new-formed connective tissue within it and to cellular infiltration of it. The former was only moderately fibrous and contained many large fibroblasts. The latter consisted of leukocytes, lymphocytes and round cells predominating, but with a heavy admixture of polymorphonuclears. Throughout this mass of inflammatory tissue ran the capillaries, much reduced in number by collapse and obliteration. Those remaining were distorted and irregular in their course, but contained a few well preserved red blood cells and leukocytes. Their endothelium could be distinguished, though in many places these cells were displaced and lay scattered through the inflammatory tissue previously mentioned.

Tubules: To one side of, and partially surrounding, the glomerulus lay the mass of the tubules which belonged to the unit. The great majority were plainly cross-sections of the proximal convoluted tubule. Except for their size—their dimensions will be given later—they had the general appearance of the normal tubule. Their lumens were somewhat more widely open, and this space was empty except for occasional masses of detritus and a few leukocytes. No definite casts were seen within them. Save for some flattening of its contours the epithelium was that characteristic of this portion of the tubule.

The tubules lay adjacent to, and touching, each other, as neither their basement membranes nor the intertubular connective tissue was increased in thickness, nor were there any collections of inflammatory infiltration between them.

Among the larger tubules were cross-sections of others, the diameter of which was about that of the normal convoluted tubule. Since the positive identification of sections of the distal convoluted tubule is at best uncertain, and since our model will definitely decide this matter for us, no detailed description and identification of these tubules is necessary at this time.

Interstitial Tissue: This may be briefly described because within the limits of the tubular mass it was entirely normal and showed no thickening or inflammatory infiltrations. Around the mass, however, there was a definite zone of scarring, so that dense fibrous connective tissue mixed with round cells and leukocytes surrounded the hypertrophied unit without encroaching on it.

Blood Vessels: Running up from the depths of the cortex was an interlobular artery from which sprang a short branch that entered the glomerulus as the vas

Fig. 2.—Section passing through the center of the hypertrophic unit; × 150. For a description see the text.

afferens. The entire vessel showed a fibrous thickening of its wall. The intima was irregularly thickened by a layer of connective tissue hyalin, but the lumen throughout its course and into the glomerular tuft was freely patent and contained well preserved, discrete red blood cells. Within the tuft the vas afferens ended in a dilatation from which the few distorted and collapsed capillaries of the tuft arose. One of these was followed from the depths of the tuft to its attachment to the capsule where it gave rise to the vas efferens. This was a thin-walled, almost capillary-like channel which anastomosed with the intertubular network so that no definite, well distinguished efferent vessel was formed. The contrast between this ill-defined atrophied channel and the prominent, greatly thickened afferent vessel was striking. No large vein was found accompanying the interlobular artery in the region contained within the model.

The Hypertrophied Unit in Plastic Form.—The completed model including the glomerulus and its vessels, the proximal convoluted tubule to the origin of its straight medullary portion, the upper cortical portion of the broad ascending limb of Henle's loop, the connecting tubule and the upper part of the collecting tubule are shown in two aspects which for the sake of description may be called the anterior (figs. 3*A* and 8*A*) and the posterior (figs. 3*B* and 8*B*).

On its anterior aspect, at the right side of the tubular mass in its lower portion can be seen the glomerulus closely attached to the short, thickened afferent vessel which springs from the interlobular artery. A portion of the atrophied efferent vessel may also be seen, and at the lower edge of the glomerulus the exit of the proximal convoluted tubule. This tubule is immediately lost in a mass of convolutions. These, greatly increased in diameter, are so closely pressed on each other that it is impossible to follow the successive loops, though in a general way it may be seen that they ascend, culminating at the apex of the mass in a greatly thickened loop (see posterior view), which then descends to end in the relatively straight terminal portion of the proximal convoluted tubule. A comparison with figure 3*C*, reproduced from Peter's monograph, will emphasize the degree of enlargement in this structure.

The actual course of the individual loops of the proximal tubule cannot be followed in the completed model, and recourse to a special method was required for this detail. A duplicate model of the proximal convoluted tubule alone was made from the original drawings. As the wax plates were built up, copper wire was threaded through the exact centers of the lumens and properly joined together as the loops of the tubule were formed. Stereoscopic roentgenograms were then taken of the entire model. Figure 8*C* shows the result, and if viewed stereoscopically the exact course of the loops may be followed, though the acuteness of their bending makes this at times difficult.

The entrance of the ascending broad limb of Henle's loop into the glomerulotubular complex is best seen in the posterior aspect of the model. Throughout the lower third of its course it lies superficially on the mass formed by the loops of the proximal convoluted tubule. At first fairly straight, it develops a series of convolutions when it reaches the level of the upper edge of the glomerulus. This tortuosity increases until the tubule disappears into the depths of the convolutions. It is this portion only which may be strictly called the distal convoluted tubule.

The tubule now reappears on the anterior surface of the model just above the glomerulus and after a few convolutions becomes the connecting tubule. This is a comparatively straight structure which, lying on the upper edge of the tubular mass, passes up and loops backward along with the culminating loop of the proximal division previously described. Here it disappears into the tubular mass

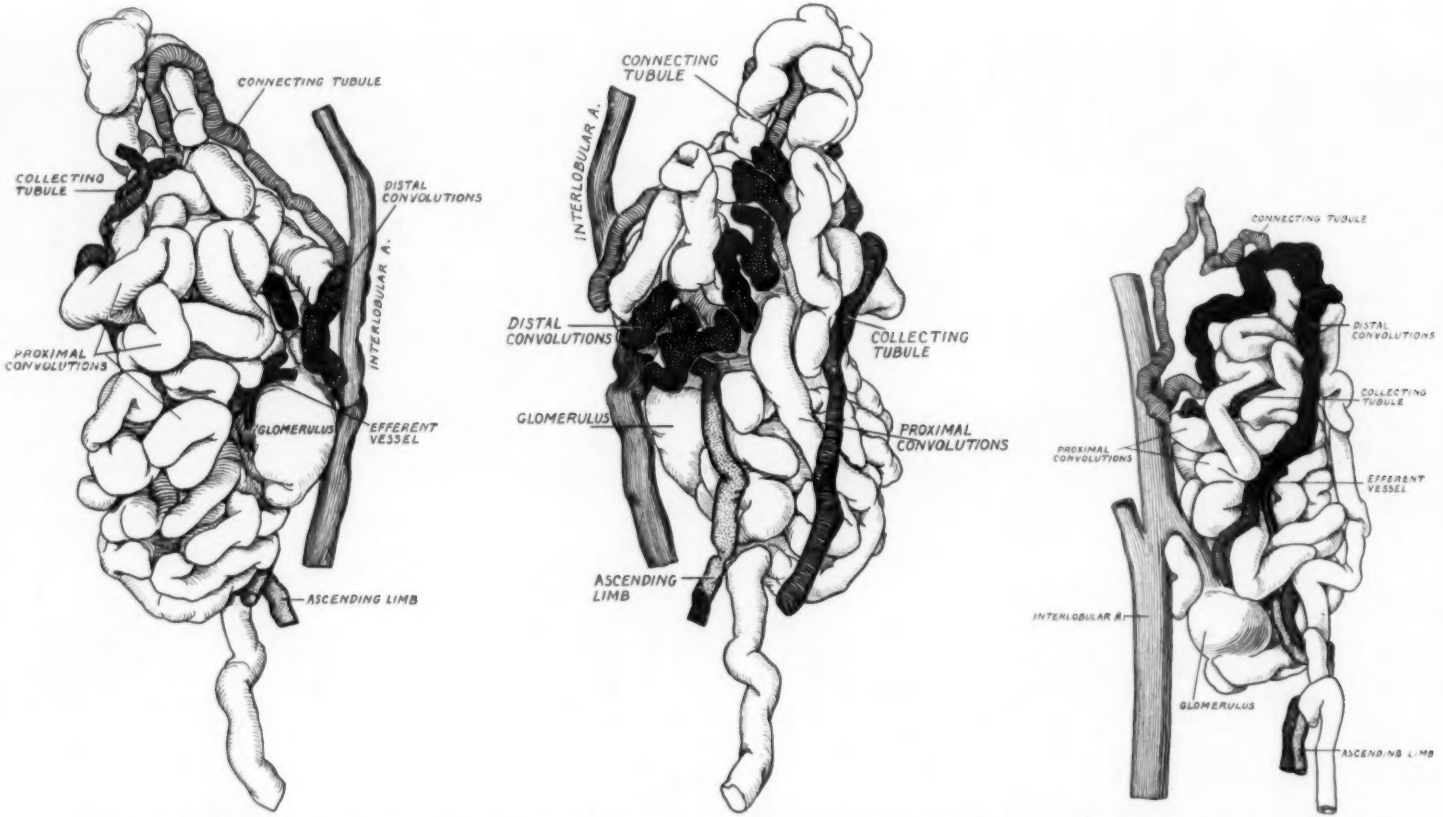

Fig. 3.—*A*, anterior aspect of the hypertrophic unit; × 50. *B*, posterior aspect of the hypertrophic unit; × 50. *C*, glomerulotubular unit of a normal kidney, redrawn from figure 37 a, plate V, in Peter: Untersuchungen über Bau and Entwickelung der Niere, Jena, Gustav Fischer, 1909; × 50.

again where it becomes the collecting tubule. This portion on its emergence descends directly toward the medulla, and may be seen on the right side of the posterior aspect of the model, where it lies superficially. On the anterior surface of the model to the left and just below the uppermost loop of the proximal convoluted tubule may be seen the cut end of the connecting tubule of another glomerulotubular unit which is joining this same collecting tubule.

Since the greater portion of the glomerulus is hidden by the loops of tubule which surround it, a separate model was made of it and its blood vessels from the original drawings (fig. 9 *A* and *B*). It is seen to be a spherical object, set closely by means of its short, thickened afferent vessel on the interlobular artery. The efferent vessel is also seen, its exit from the capsule lying in the center of the tuft as shown in figure 9 *A;* from this point it continues in both directions as a thin-walled, capillary-like channel. The union with an adjacent intertubular capillary can be seen on the right upper edge of the capsule. From the lower part of the glomerulus is seen the origin of the proximal convoluted tubule, which turns at a right angle almost immediately after its emergence.

The Atrophied Glomerulotubular Unit.—For the illustration of an atrophied unit an area of scar tissue in the middle of the series was selected which enclosed within its fibrous tissue a shrunken glomerulus and tubules. The group was selected purposely, since its glomerulus was not completely fibrosed, but contained an occasional capillary. Neither was the lumen of the shrunken tubule about it completely obliterated. The unit lay at a distance of 3 mm. from the hypertrophied unit previously described and somewhat deeper in the cortex (fig. 1 *B*). A section through the center of this mass showed the following details (fig. 4):

Glomerulus: This was much smaller than that previously described and was even reduced in size below that of the normal, as will appear later when measurements and volumes are considered. On section the tuft was found almost to fill the capsule. Its structure was similar to that of the enlarged tuft, since it was infiltrated with connective tissue fibroblasts, inflammatory leukocytes and proliferating endothelial cells. There was, however, a greater amount of collagen, which in some places was densely thickened to form hyaline masses. The greater part of the capillary bed was thus obliterated, though a few tortuous blood channels still existed. These could be traced to an afferent and an efferent vessel. The capsular space, though existent, was almost completely obliterated by fibrous adhesions. It communicated, however, with the proximal convoluted tubule.

Tubule: In the dense connective tissue that lay about the glomerulus and which extended upward into the cortex were the cross-sections of many shrunken and distorted tubules. These varied greatly in size and shape. Some were the diameter of the smaller connecting tubules of the previously described unit, and in these the epithelium was fairly typical in appearance, and the lumen, though narrow, was regular in shape. Many others, however, were very small, some consisting of a group of a few shrunken epithelial cells surrounded by a membrana propria and containing an irregularly distorted minute lumen. The tubules were widely spaced, their cross-sections appearing as if scattered at random in the inflammatory fibrous tissue of the scar.

As a result of the growth of the inflammatory tissue and the resulting changes in the tubules, there was nothing morphologically typical in any of them that would permit speculation as to what might be proximal convoluted tubule and what some other portion of the unit. The effect of this complication on our technical procedure will appear later. However, a fixed point of departure for the tracing of the tubule cross-sections could be definitely found in the exit of

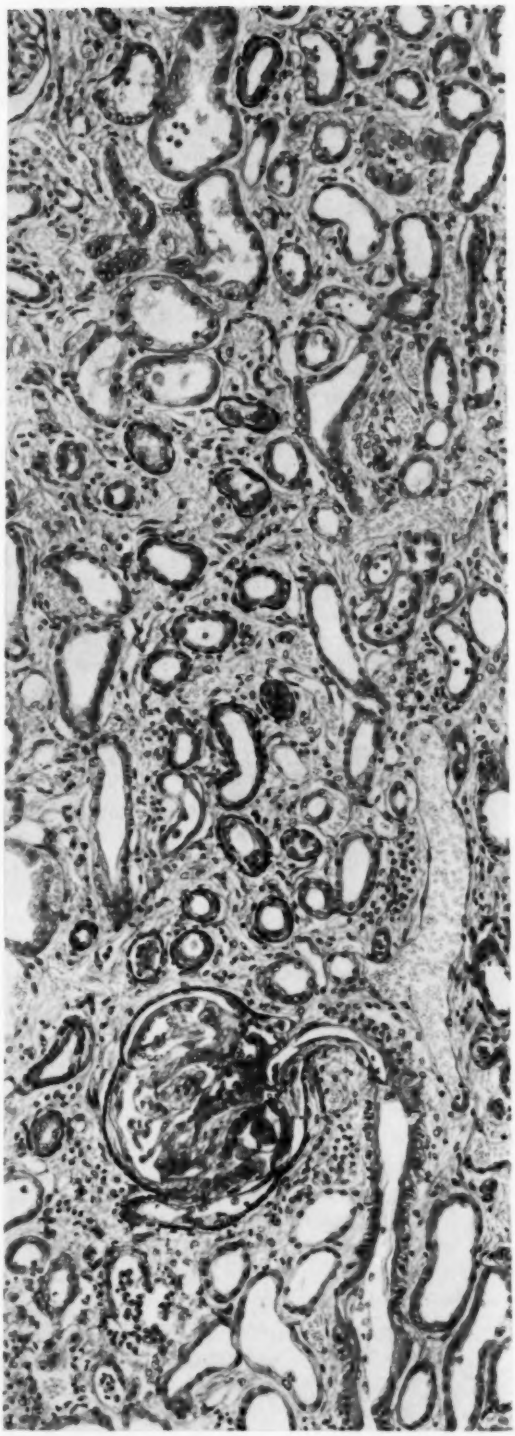

Fig. 4.—Section passing through the center of the atrophied unit; × 150. For a description see the text.

the proximal convoluted tubule from the glomerular capsule. It is seen in figure 4 as a markedly shrunken tortuous channel the endothelial-like atrophied epithelium of which lines a narrow but definite lumen.

Interstitial Tissue: The delicate connective tissue reticulum that forms the intertubular tissue of the normal kidney was profoundly changed. An extreme proliferation of it had occurred, so that a dense, almost hyaline scar tissue composed of fibroblasts and collagen fibrils, all heavily infiltrated with round cells and a scattering of polymorphonuclear leukocytes, formed wide bands which separated and surrounded the tubules and glomerulus.

Blood Vessels: The interlobular artery was seen in the section running up from the depths of the cortex and passing the glomerulus. It was somewhat tortuous and its wall was considerably thickened. The lumen, in spite of an irregular fibrous thickening of the intima, was still entirely patent and contained well preserved red blood cells that apparently were circulating in it. From the interlobular artery sprang the short, greatly thickened afferent vessel, the relatively wide lumen of which narrowed abruptly on its entrance into the tuft. Here it lost itself in the tortuous channels of the capillary bed. We were not able definitely to trace all these channels, though they were few in number, because many were composed of narrow slits the atrophied endothelium of which caused them to be indistinguishable from connective tissue spaces. However, it was easy to find the larger channel which on its exit served as the vas efferens. This was a capillary-like vessel containing well preserved red blood cells, that anastomosed a short distance from its exit with the intertubular capillary network. Accompanying the interlobular artery was a large venous channel, and into it a branch of the network was followed.

The Atrophied Unit in Plastic Form.—In the preparation of the model of the atrophied unit a serious complication resulted from the abnormal appearance of the distorted tubules that lay in the connective tissue scar, for it was found to be entirely impossible to identify, even provisionally, any cross-section as that of any particular part of the tubule. When the tracing of the tubule was begun it was also found that the distortion had produced a marked irregularity in the twisting of the loops. This, combined with the sudden constrictions in its diameter that appeared and disappeared from one section to the next, made the task of following the course of even the proximal tubule much more difficult than in the previous model. The end-result was that the distal tubule, including the ascending limb of Henle's loop, the connecting tubule and the collecting tubule, could not be positively identified, and it was therefore thought better to omit them from the model. The final completed presentation shows, therefore, only the glomerulus and its vessels and the proximal convoluted tubule. It is seen in two aspects: in figures 5 *A* and 9 *C*, the so-called anterior view; in figures 5 *B* and 10 *A*, the posterior view.

At the lower edge of the mass of the tubular convolutions is the glomerulus. In the anterior view it is almost entirely free. At its lower left edge can be seen the origin of the proximal convolution. In the posterior view the upper half of the glomerulus is hidden by loops of the tubule. In its general shape as seen in the figures, the capsule is neither greatly diminished in size nor distorted. When viewed at right angles to these aspects, however, it is found to be markedly flattened by the connective tissue which surrounds it, so that instead of possessing its normal spherical shape it is almost lenticular. Its volume, to be considered later, is therefore considerably reduced.

From its origin in the glomerulus, the proximal convoluted tubule may be seen in the anterior view of the model proceeding upward in irregular and

tortuous loops at the left side of the glomerulus. It then turns directly at a right angle toward the right, reaching a point above the center of the glomerular mass, where it again turns upward soon to be lost in the complex tangle of its convolutions. These tortuous loops are especially well shown in the posterior view. A striking feature of the appearance of this tubular complex is not only the narrowness and dilatation of the looped tubule but the spacing of its convolutions, which are so widely separated that one can easily look into the very center of the model. These spaces in actual conditions were filled with the inflammatory fibrous granulation tissue which comprised the scar. In the upper third of the tubular mass, the tubule finally frees itself and passes directly upward to form the culminating apical loop which, doubling abruptly backward, descends

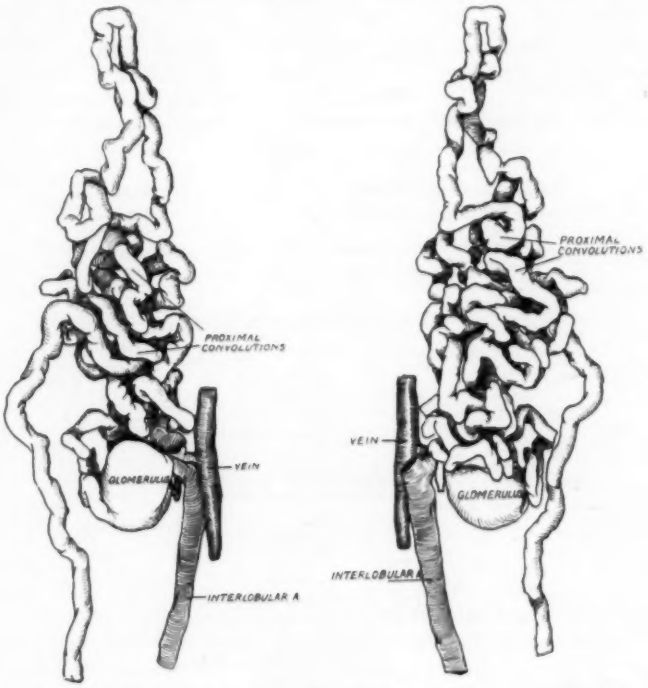

Fig. 5.—*A*, anterior aspect of atrophied unit; × 50. *B*, posterior aspect of atrophied unit; × 50.

with a few sudden kinkings to pass on the left of the glomerulus and so to form the terminal part of the proximal convoluted tubule (anterior view). A comparison of this distorted and irregularly shrunken tubule with Peter's representation of the normal (fig. 3*C*) emphasizes the amount of change that has occurred.

The exact course of the tubule is shown in the stereoscopic roentgenograms of a duplicate model made as previously described with a copper wire running continuously through the center of the tubule. Even with this simplification and with the aid of stereoscopic vision it is almost impossible to follow the course of the distorted loops (fig. 10*B*). A comparison may be made with the loopings of a normal proximal convoluted tubule as shown by Peter.[6]

6. Peter,[4] plate V, fig. 47 b.

The details of the entrance and exit of the afferent and efferent vessels are shown in a duplicate model of the glomerulus (fig. 9 *A* and *B*). From the interlobular artery a greatly thickened short afferent vessel plunges directly into the capsule of the glomerulus. In figure 9 *A* the exit of the efferent vessel is visible. It is a thin-walled channel which unites almost immediately after its exit with a branch of the intertubular network. A communication with the large venous channel which accompanies the interlobular artery is plainly seen. The exit of the atrophied proximal convoluted tubule is also visible.

Comparative Measurements.—No attempt has been made in the description so far to give any quantitative data on the dimensions of the various portions of the glomerulotubular units. A general idea of the relative mass of the entire complex in the two cases as compared with that of a normal tubule, as illustrated

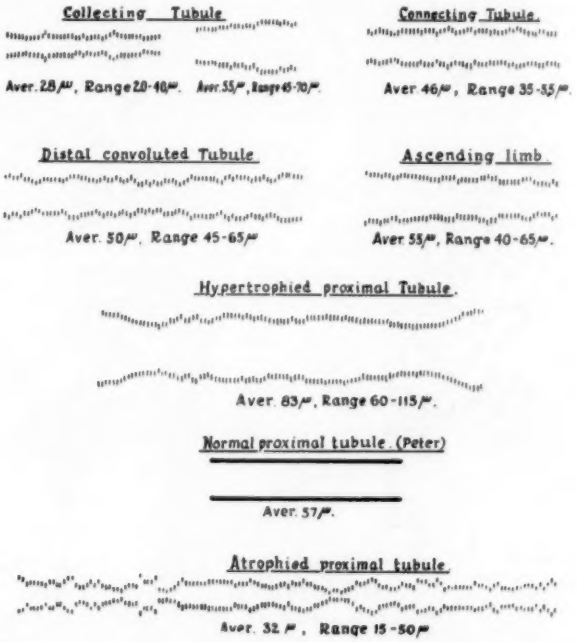
Collecting Tubule
Aver. 28 μ, Range 20-40 μ. Aver. 55 μ, Range 45-70 μ.
Connecting Tubule.
Aver. 46 μ, Range 35-55 μ.
Distal convoluted Tubule
Aver. 50 μ, Range 45-65 μ
Ascending limb
Aver. 53 μ, Range 40-65 μ.
Hypertrophied proximal Tubule.
Aver. 83 μ, Range 60-115 μ.
Normal proximal tubule (Peter)
Aver. 57 μ.
Atrophied proximal tubule.
Aver. 32 μ, Range 15-50 μ

Fig. 6.—Diameters of various portions of tubules from normal, atrophied and hypertrophied units.

by Peter, can be appreciated by a comparison of figures 3 *A* and *C* and 5, which are all represented in a magnification of 50 times. The exact measurements of the diameters of various portions of the tubules and of the glomeruli were made from the original drawings by which the models were constructed. In the case of the hypertrophied unit this procedure was easily followed, since all the structures were regular in their shape. But with the tubule of the atrophied unit the measurements varied so greatly, even from section to section, on account of the sudden constrictions in its surface, that individual figures had little meaning. In the latter case, therefore, successive measurements of diameter were plotted on cross-section paper so that a typical portion of an idealized tubule is represented that presents an absolutely straight direction but with all the irregularities of its contour (fig. 6). On the same scale are shown the even

contours of a normal proximal convolution and other portions of the hypertrophied unit.

The increases in diameter shown in figure 6 are striking, but even greater contrast might be found if the cross-section area of the tubules in the three cases, hypertrophied, atrophied and normal, were compared. But such a calculation is impossible with the atrophied unit, so that to afford some quantitative figure comparable in all three cases determination of the volume of the complete proximal tubule from its origin in the glomerulus to its terminal medullary portion seemed desirable. This required the determination of the length of the tubule, a datum that was obtained by melting the wax from the copper wire of the two duplicate models and straightening it. When this was done, it was found that the hypertrophied proximal convoluted tubule measured 492 cm., representing an actual length in the original organ of 2.46 cm. The tubule from the atrophied unit measured 307 cm., or 1.53 cm. in the actual kidney. The average length of a normal proximal convolution as given by Peter is 1.4 cm., the upper limit having been observed at 1.7 cm.

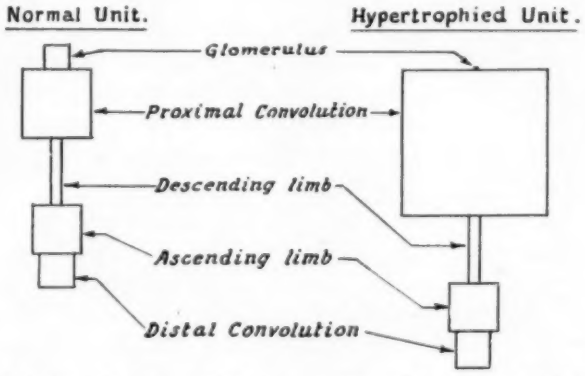

Fig. 7.—Relative size of surfaces in normal and hypertrophied glomerulotubular units.

The volume of a measured portion of the terminal part of the proximal convoluted tubule of each model was then determined by immersion in water and the total volume for the entire length calculated. The volume of the hypertrophied tubule was 0.16 c. mm.; that of the atrophied tubule, 0.015 c. mm. As calculated from a uniform diameter and the extremes of length, the volume of a normal proximal convoluted portion may be from 0.026 to 0.04 c. mm. The volume of the glomeruli in the two units was also determined by immersion. The hypertrophied glomerulus measured 0.009 c. mm.; the atrophied, 0.003 c. mm. The normal glomerulus, by calculation, has a volume around 0.004 c. mm. The significance of these measurements will be deferred until the comment.

The final quantitative measurement was done to determine if the increase in size, in both diameter and length, of the proximal convoluted tubule in the hypertrophied unit was due in part to an increase in the number of its constituent cells. For this purpose nuclear counts were made on those perfectly round cross-sections that had passed at right angles through the tubule. To avoid the danger of counting portions of the same nucleus in succeeding sections, only every sixth section was used. The average nuclear count in 284 cross-sections counted was 8.47, a figure well above the average of 4 which is usually given for this portion of the tubule.

No measurements of the size of individual cells were made on our material, since in a tube that is even slightly distended it cannot be assumed that the resulting distortion has affected all the diameters of a cell which forms a part of its wall in any regular or predictable manner.

COMMENT

A summary of results as they regard the specific morphologic aspects of the problem may be briefly given.

In the case of the hypertrophied unit it has been seen that the change from original conditions was a relatively simple one so far as the tubular elements were concerned, consisting solely in an increase in the size of the proximal convoluted tubule. The other elements of the tubular complex remained unaffected, nor were there any significant alterations in the topographic relation of the various parts to each other. Hyperplasia, by an increase in the number of cells in the proximal tubule, played a considerable part in the increase in tissue. Not only was there an increase in the diameter of the proximal tubule but there was a definite increase in its length, and as a result the tubule was thrown into more acute loops and kinks than are normally observed. This increase in the length of the proximal convoluted tubule in compensatory hypertrophy has been studied experimentally.[7]

In the case of the atrophied unit the decrease in the size of the proximal tubule was equally definite. This reduction was shown by measurements of its diameter, and these varied markedly owing to the irregular constrictions in it that had been produced by the contracting scar tissue. It seems unlikely, however, that there could have been much decrease in its length, since this was still greater than the average for the normal proximal convoluted tubule. It is possible, however, that the tubule examined was an exceptionally long example of its type, and on comparison with the longest proximal tubule on record, 1.7 cm.,[4] it is evident that there may have occurred a shortening of about 20 per cent.

Besides the effect on the proximal tubule we can also be certain, even in the absence of a direct demonstration in plastic form, that the atrophy, unlike the hypertrophy, affected the distal portions, for a glance at figure 6 shows that there were no cross-sections of tubules contained in the area of the glomerulotubular complex which approached in size the original structures. Besides the effect on both portions of the convoluted tubule, another contrast with the hypertrophied unit was found in the fact that the topographic arrangement of the atrophied proximal convoluted tubule differed strikingly from that of the normal. This was the result of the connective tissue proliferation, which as well as constricting the diameter of the tubule had separated widely the loops that form

7. Peters, E.: Ztschr. f. Zellforsch. u. mikr. Anat. **8**:63, 1928.

the tubular complex. The character of the epithelium of neither the hypertrophied nor the atrophied proximal convoluted tubules was entirely normal. In the former hyperplasia had produced some morphologic irregularity in the cells, while in the latter atrophy and regeneration had replaced the lining with an entirely atypical epithelium.

In comparing the glomeruli of the two units but one difference was noted, that of size. Their structure was similar and was largely the result of inflammatory connective tissue proliferation within the tuft and the capsule. That one was large and the other small may have been due to the fact that the inflammatory proliferation occurred in tufts which were previously either hypertrophied or atrophied, or it may have been the result of the changes in the growth of the inflammatory tissue. Since a preliminary increase in size may be followed by shrinkage of collagen and a consequent terminal decrease, it is difficult to determine how much hypertrophy or atrophy per se had to do with the sizes of the two glomeruli. In both, the great majority of the tuft capillaries and the greater part of Bowman's space were obliterated, and the original free surfaces, which must be of great importance in glomerular activity, were greatly reduced.

The glomerular circulatory systems in the two models were essentially similar. In both, a sclerotic but patent interlobular artery gave rise to a greatly thickened afferent vessel which entered the tuft and broke up into a few distorted capillaries. In both a very thin-walled efferent vessel led from the tuft and entered the intertubular network. Well preserved, discrete red blood cells could be seen throughout all these vessels, so that it is reasonable to suppose that the circulation through them was intact. In neither case was Ludwig's anastomosing branch present. The marked discrepancy in size of the afferent and efferent vessels, which normally are more nearly equal, is understood if one considers that the full blood pressure, which was abnormally high, operated on the dilated afferent vessel, while capillary obliteration in the tuft allowed but little pressure or blood to pass through, with a consequent collapse of the efferent vessel.

Two general conclusions may be drawn from the observations here reported. The first concerns the anatomic aspect of the problem.

The two types of glomerulotubular complex that we have described comprise the two essential architectural units from which the kidney in chronic Bright's disease is built. As we have shown,[8] the architectural change that occurs in the end-stages of the disease may produce two types of metallactic change. These we termed diffuse and patchy metallaxis from their striking histologic features. In a diffuse metallaxis the kidney is built up of predominating units of the atrophic

8. Addis and Oliver,[3] p. 165.

type that we have figured, and we have described cases in which every complex in the contracted organ was of this type.[9] In patchy metallaxis among a certain number of such atrophic units are found scattered hypertrophied units.[10] Any kidney as it is found in the end-stages of Bright's disease may therefore be reconstructed in its essential characteristics from the two types that we have demonstrated in plastic form.

The question may be asked as to what determines whether the metallaxis is to be patchy or diffuse. That the cause of the difference is not to be found in "focal" and "diffuse" forms of glomerulonephritis is obvious from the fact that both atrophied and hypertrophied units were involved by the inflammatory process. Two factors present themselves as possibilities. First, differences in the state of the vessels that supply the diseased unit may determine whether a progressive or a regressive change occurs in its tissue, the latter being the result of some circulatory deprivation that complicates the essential inflammatory processes. But this is definitely not the determining factor, for, as we have shown, the vessels in the two units, hypertrophied and atrophied, were identical. The second possibility must remain for further examination. And this is that the atrophy, being a direct result of the contraction and pressure of inflammatory connective tissue fibrosis, is determined in the last analysis by the factors which cause this fibrosis and influence its distribution.

The second general consideration is perhaps the more important but one that unfortunately at present seems impossible of complete solution, and that is the functional significance to the individual of these two types of change that may occur in the glomerulotubular units. There is no question that the hypertrophic and atrophic change may be respectively considered a progressive and a regressive process. One is at once tempted, therefore, to think of the former as a method of repair and compensation with some added corollary assumption of hyperfunction.

In another place we have discussed at some length the difficulties that arise when an attempt is made at a direct correlation of quantitative measurements of morphologic and functional data.[11] This method has been used in physiologic problems, and it has been suggested that it might also be applied to pathologic interpretations on the assumption that "pathology shows in general only quantitative alterations of normal processes as the basis of the disease."[12] Our criticism has been that, in the first place, the observational error in such attempts is so enormous

9. Addis and Oliver,[3] p. 206, plate VII a.

10. Addis and Oliver,[3] p. 290, plate XXIV a.

11. Addis and Oliver,[3] p. 105.

12. Pütter, A.: Die Drei-Drüsentheorie der Harnbereitung, Berlin, Julius Springer, 1926, p. 168.

that little is left of quantitative significance, and, what is of even greater importance, that the assumption of an occurrence of only quantitative variations from normal in the pathologic state is entirely unwarranted. A tubular cell in a state of cloudy swelling may weigh or measure several times that of a normal cell, but whether the functional ability of the cell is increased or decreased is not known. Similar instances could be cited almost indefinitely as reasons why we do not care to extend our powers of deduction on the meager morphologic quantitative data that we have acquired. It is for no purpose of generalization, therefore, that we compare these results with those of Pütter, whose ingenious method [13] illustrates the relative proportions of the various parts of the normal renal unit, but only because such a presentation shows the contrast in the quantitative structural relations in the two cases so strikingly.

The normal relations of surface of the various parts of the renal unit as calculated by Pütter are shown in figure 7. On the same scale the hypertrophied unit is shown with its barely existent glomerular surface, its enormous proximal tubule surface and its remaining portions of normal size. In regard to the determination of the latter, we calculated the surface area of the distal convolution from observed data. The cortical portion of the broad ascending limb of Henle's loop was of normal size, and since there were few or no significant pathologic changes in the medulla, it seemed reasonable to assume that there was no great departure from the normal dimensions in the portion of the loop, either descending or ascending, which was contained within it.

The diagram at once calls to mind an old dictum of renal pathology that obliteration of the glomerulus is followed by inactivity atrophy and collapse of the tubule. Though there was not absolute obliteration in the case studied, this condition was approached closely; yet not only was the tubule hypertrophied, but its distended lumen gave evidence that some sort of fluid was contained within it. A glance at a section of the kidney in this case shows that the same is true of all the hypertrophied units. In lower forms with aglomerular kidneys, the tubule is able to perform varied functional activities, and it is not beyond the realm of possibility that it does so to some degree under pathologic conditions in the mammalian organ. A further study of such "aglomerular" tubules in chronic Bright's disease is being undertaken.

If direct deduction from correlations of quantitative normal and abnormal morphologic data is at present a precarious procedure, it nevertheless seems reasonable to draw certain general conclusions from observations made on the disease processes themselves. An analysis of many cases [14] has shown that those who suffer from a Bright's disease characterized by a diffuse metallaxis and who die of uremia do so, as a

13. Pütter,[12] p. 92, fig. 6.

14. Addis and Oliver,[3] tables XLIII and XLIV.

rule, in the active stage before they reach the definitely terminal stage of the disease. Those with Bright's disease of a patchy metallactic nature usually survive until the processes have run their active course and subsided and the terminal stage has been reached; then they, too, die of uremia. The hypertrophic processes may therefore allow the patient to live a sufficient time for the disease to complete its evolution, but they seem to offer at present no teleologic advantage.

But the advantage is plainly there if only it could be seized on. It may be that renal failure eventually supervenes in these persons only because the noxa that is producing the inflammatory process continues to reach the hypertrophying units and so destroys them, and the last reserve is depleted. Instead of a conclusion of pessimism, therefore, the appreciation of the degree and nature of the hypertrophic process, even as it is observed in the fatal case, offers a definite note of optimism. For a mechanism of repair is actively functioning under these unfavorable conditions and might be successful if it could be encouraged and allowed to proceed in its natural direction, for we have seen that under its influence one proximal convoluted tubule may assume the physical size of six normal structures. A way for an attack on the problem of treatment is thus pointed out. Attempts to remove the noxa from the circulation have long been tried without great success. Could these efforts be supported by a stimulation of the hypertrophic processes? The effect of diet on experimental renal hypertrophy may afford a clue to the answer to this question.

Fig. 8.—*A*, stereoscopic view of the anterior aspect of the hypertrophic unit shown in figure 3 *A*; × 35. *B*, stereoscopic view of the posterior aspect of the hypertrophic unit shown in figure 3 *B*; × 35. *C*, stereoscopic roentgenogram of the hypertrophied unit showing the course of the proximal convoluted tubule; × 35.

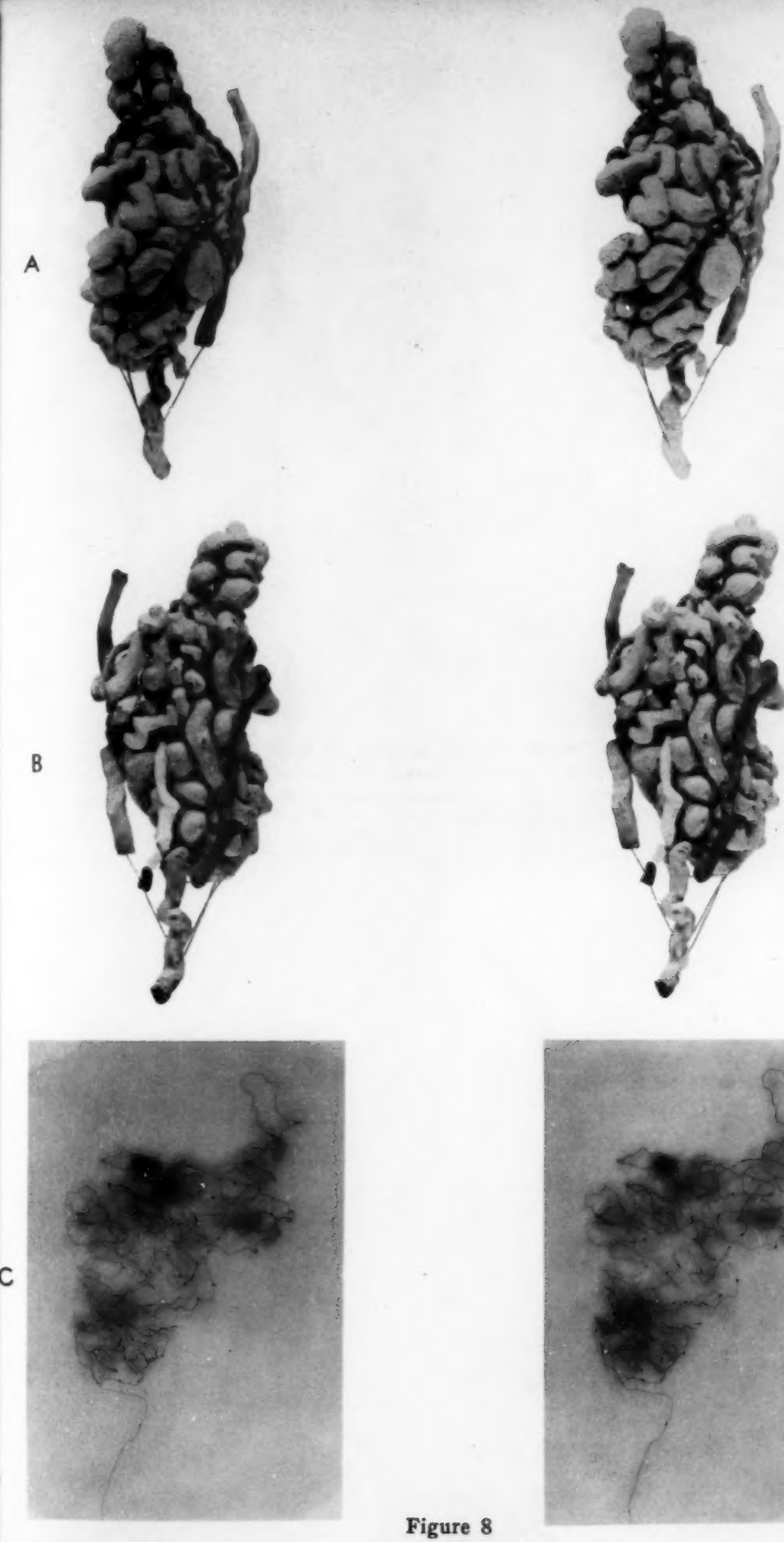

Figure 8

Fig. 9.—*A*, stereoscopic view of the glomeruli from the hypertrophied and atrophied units; × 50. *B*, obverse stereoscopic view of models of the glomeruli from the two units; × 50. *C*, stereoscopic view of the anterior aspect of the atrophied unit shown in figure 5 *A*; × 35.

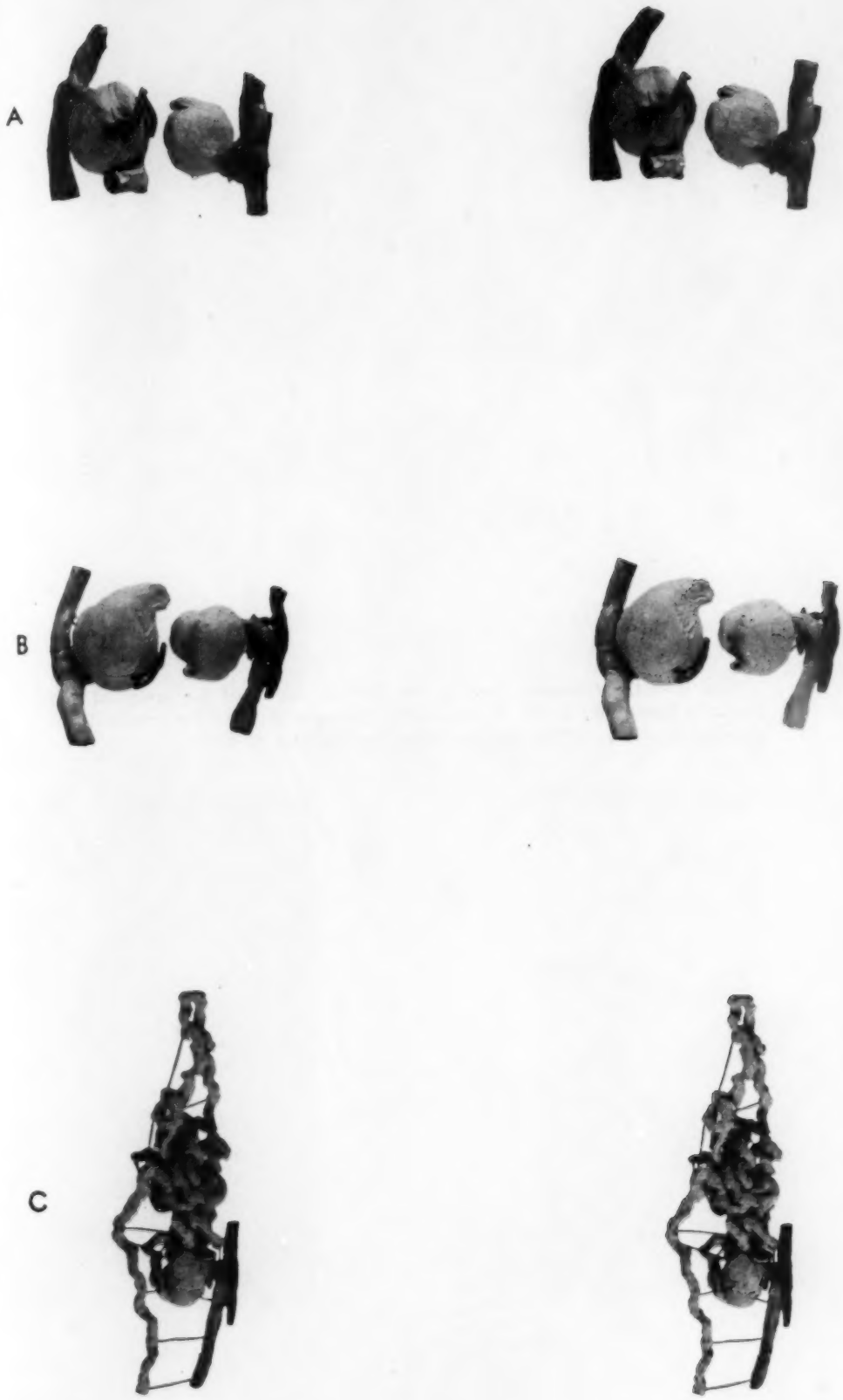

Figure 9

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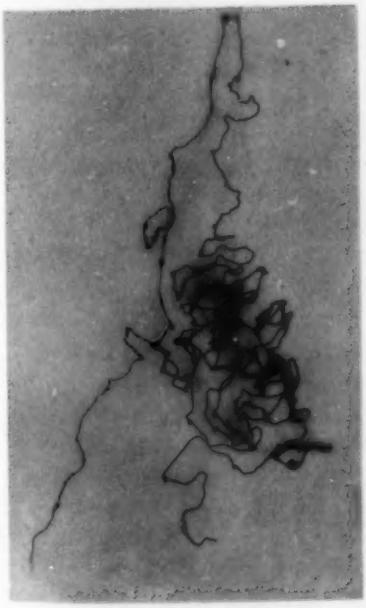
Fig. 10.—*A*, stereoscopic view of the posterior aspect of the atrophied unit shown in figure 5 *B*; × 35. *B*, stereoscopic roentgenogram of the atrophied unit showing the course of the proximal convoluted tubule; × 43.

A

B



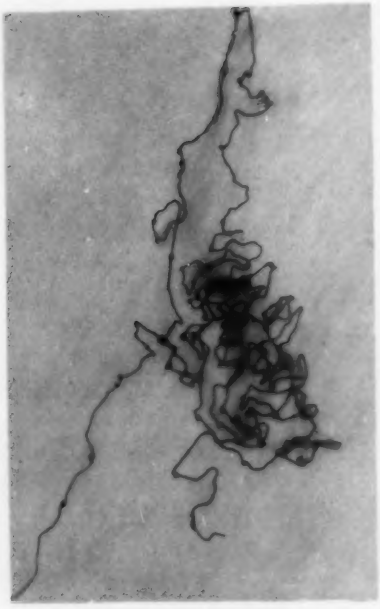


Figure 10

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TUMORS OF THE SUPRARENAL GLAND

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BALTIMORE

Primary tumors of the suprarenal tissues are not common, but a variety of clearly defined neoplasms arising in the suprarenal gland have been described. Apparently, however, such growths have been little emphasized in the literature, and unfamiliarity with them is responsible for the persistent error of ascribing so-called renal hypernephromas to this organ. In calling attention to the outstanding characteristics of these primary tumors of the suprarenal gland it is hoped that further case reports on these relatively rare tumors will be stimulated, and that renewed interest will aid in dispelling much of the confusion existing concerning the so-called suprarenal rest tumors.

Specific tumors of suprarenal cells are usually divided into cortical and medullary types. The cells of origin of the two groups have an entirely different developmental history, and in some of the lower vertebrates such as the amphibia and fishes, the two cell groups, cortical and medullary, remain separated as two distinct organs. Comparative anatomists in emphasizing the distinct origin of these two cell types have chosen the name "interrenal organ" for the lipoidal cells which comprise the suprarenal cortex and the name "suprarenals" for the chromaffin cells that form the suprarenal medulla. The interrenal, or cortical, tissue is derived from the mesoderm and is contemporary in its development with the mesonephron. The embryonal source is thus closely associated with the urogenital cell mass. On the other hand, the chromaffin cells of the suprarenal medulla (suprarenal organ) are derived from the ectoderm and have a common origin with cells comprising the sympathetic nervous system. The pathologic behavior of cortical and medullary tumors of the suprarenal gland bears out this twofold mode of origin, the more rapidly growing cortical tumors being accompanied by changes in the sex characteristics, while many of the medullary tumors are identical in microscopic structure with the neurogenic tumors found elsewhere in the body of the chromaffin, or sympathetic, structures.

The most frequent tumors of the suprarenal cortex are the benign cortical adenomas, which are incidental findings at autopsy and rarely give clinical indication of their presence. Carcinoma of the suprarenal

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From the Surgical Pathological Laboratory of the Johns Hopkins Hospital and University.

This study was aided by a grant from the Anna Fuller Fund.

cortex is much rarer and is accompanied by clinical manifestations affecting the secondary sexual characteristics of the patient. The medullary tissue of the suprarenal gland which secretes epinephrine is rarely the source of neoplastic change, but may give rise to chromaffin carcinoma characterized clinically by alterations in the blood pressure. The largest and most varied group of medullary tumors take origin from sympathetic nerve elements located in the medulla. These nerves, however, also traverse the cortical substance, so that tumors arising in these structures are not necessarily medullary. These tumors of sympathetic neural structure are usually malignant and vary from the more undifferentiated sympathoblastoma (an extremely small-celled tumor) through the paragangliomas with cells of intermediate size to the large-celled ganglionic tumors. While most common in the suprarenal gland, they may occur in sympathetic nerve tissue anywhere in the body and tumors similar to the more undifferentiated types are not uncommon in the retina and cerebellum.

The present study deals only with the primary tumors arising in suprarenal tissues. While all varieties of these primary tumors have been described in reports in the literature, a well defined conception of their pathology and histogenesis as a group is generally lacking.

CORTICAL TUMORS

Benign Cortical Adenomas.—Circumscribed nodules of the mature cortical cells are frequently found at autopsy projecting from or overlying the surface of the suprarenal gland. Some writers believe that they are present in nearly one third of all cases examined at autopsy, regardless of age, sex or cause of death. The size of these adenomas varies from that of a pea to that of an egg, and their color is a mottled brown and yellow. The structure is often lobulated. It is difficult to distinguish between cortical adenomas, accessory interrenal bodies and localized hypertrophy, but the larger nodules are usually definitely neoplastic.

Microscopically, the tumors are composed of an orderly or disorderly arrangement of cortical cells, which may or may not show the same order of zones that is found in the normal suprarenal cortex. Many of the cells show a high lipoid content, and masses of such lipoidal cells with degenerating cytoplasm and small dense nuclei are frequently seen surrounding a capillary network. Other cells of the cortical type may grow in cordlike arrangement or in glomerular masses or in a reticular manner, recalling the zones of the normal suprarenal cortex. These cells have a definite amount of clear cytoplasm; the nuclei are fairly densely packed with chromatin and may be fairly large in size and have an asymmetrical location. Here and there in the section the cells may be grouped in an acinar arrangement, and deposits of chromaffin pigment can be seen. The distinguishing characteristics of the

adenomas are the definite cortical cells, the tendency to lipoidal degeneration, the marked capillary network, the pigment deposits and the cords or bundlelike arrangement of the cells (fig. 1 *A*).

Cortical Carcinomas.—Less differentiated cortical tumors are rare in the suprarenal glands, and unlike the benign adenomas they usually

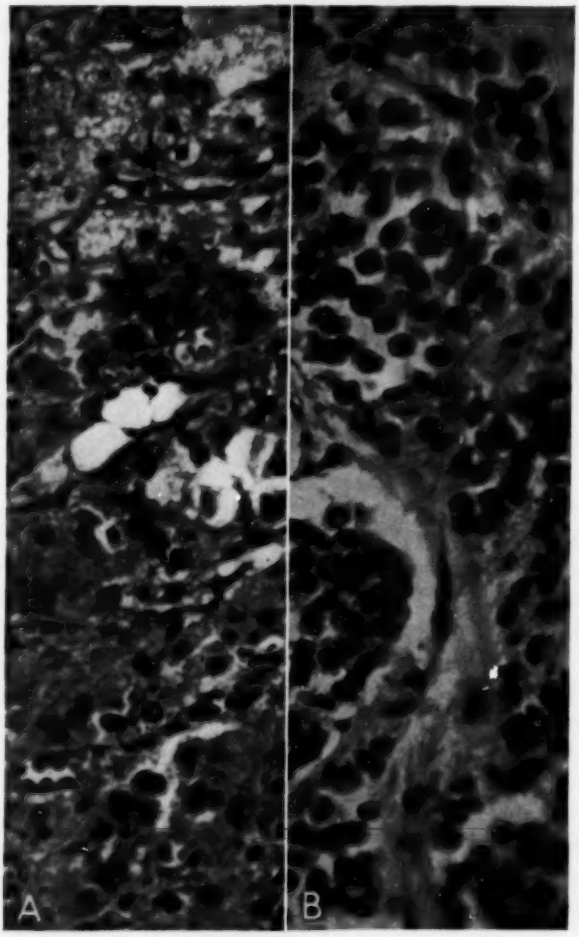

Fig. 1.—*A*, high power photomicrograph of benign adenoma of the suprarenal cortex. Small, dense nuclei are surrounded by a fairly large amount of cytoplasm, which undergoes foamy degeneration.

B, high power photomicrograph of carcinoma of the suprarenal cortex metastasizing to the liver. The nuclei are hyperchromatic, and the cytoplasm is much reduced in amount. The arrangement of cells tends to simulate that of the embryonal carcinomas seen in the testis and the ovary, and the tumor is accompanied by disturbances in the sexual characteristics of the patient. See figure 2.

produce definite symptoms. In describing them it is important to rule out the so-called hypernephromas which are sometimes considered to be suprarenal carcinomas arising from misplaced cortical cells in the kidney. The majority of the so-called hypernephromas are renal carcinomas, often of papillary type with cells containing an abundance of glycogen. This papillary structure and the glycogen content distinguish these so-called hypernephromas from cortical carcinomas of the suprarenal gland.

The clinical course of malignant suprarenal cortical tumors is usually rapid and fatal. Changes in the sex characteristics predominate, and symptoms of Addison's disease are rarely seen. The sex changes have been referred to by Gallais [1] as the suprarenal-genital syndrome. The symptoms are precocity in sexual development and pseudohermaphroditism, both of which are most frequently met with in females. In male patients feminization and a homosexual tendency may occur. Apparently these sex changes may take place in the presence of either benign or malignant cortical tumors, but the most rapid and marked changes in the sexual sphere are caused by the malignant growths. The fully developed syndrome in females has sometimes been called hirsutism and consists in obesity, hypertrichiasis and the growth of whiskers or of a mustache on the face.

The malignant suprarenal cortical tumors usually attain a fairly large size varying from that of an egg to that of an orange, and are rapidly invasive and destructive. The bulk of the tumor may be consistent and grayish but nearly always there are present soft hemorrhagic areas characteristically mottled red and yellow. These tumors are prone to invade the kidney and the retroperitoneal tissue, to extend up the large renal veins and to metastasize to distant organs, particularly to the liver and the lungs. Microscopically malignant tumors of the suprarenal cortex grade imperceptibly toward benign cortical adenomas, on the one hand, and, on the other, toward the more outspoken malignant forms with prominent nuclei and many mitotic figures. Those resembling benign adenomas are usually termed adenoma malignum; those with more malignant cellular characteristics, diffuse carcinoma. Adenoma malignum of the suprarenal cortex resembles the benign adenoma in its tendency to grow in cords or fasciculi, but is unlike the benign adenoma in that signs of lipoidal degeneration in the cytoplasm are not prominent, and in that the ratio of nucleus to cytoplasm is altered in favor of the nucleus. The nuclei show increased chromatin content and moderately vesicular forms, but mitotic figures are rare. The cytoplasm is of fair but not conspicuous amount.

The malignant characteristics of diffuse carcinoma of the suprarenal cortex are more outspoken. The nuclei are prominent and hyper-

1. Gallais, Alfred: Syndrome genito-surrénal, Thèse de Paris, 1912.

chromatic and contain many mitotic figures. The cytoplasm is less in amount and forms a small ring about the nucleus. The cells tend to grow in sheets or in lobulated masses separated here and there by a small amount of stroma resembling in arrangement the embryonal carcinomas with lymphoid stroma occurring in the testis and ovary. The primary tumor shows necrosis and degeneration at the center of the specimen, but the metastases maintain a more cellular and diffusely growing character (fig. 1 *B*). The malignant tumors of the suprarenal cortex as a group are distinguished from the medullary tumors of the ganglionic or of the chromaffin type by the absence of giant tumor cells and similar bizarre nuclear forms. On the other hand, the cells are larger than the undifferentiated cells of the sympathoblastomas of the suprarenal medulla.

The case of carcinoma of the suprarenal cortex described in the following paragraphs presents many typical features.[2]

A white woman, aged 57, who was admitted to the hospital in April, 1931, complained of weakness and pain between the shoulders. For six months she had noticed edema and puffiness of the hands and ankles, and her condition had been diagnosed myxedema and treated with thyroid extract. On examination, she showed marked virilism, a beard and increased growth of hair appearing on the arms and legs (fig. 2). At the fifth thoracic vertebra, there was a marked gibbus, which was tender to pressure. There was hypertension (190 systolic and 88 diastolic) with pitting edema over the ankles. A roentgen examination revealed destruction of the fifth thoracic vertebra, thought to be metastatic in origin, and areas of bone destruction in both femurs. There was slight secondary anemia. She was given roentgen treatment, but sank rapidly and died with a terminal skin infection resembling erysipelas.

At autopsy, both the abdominal and the pleural cavity contained free fluid. The liver contained many metastatic nodules. The retroperitoneal lymph nodes were enlarged and contained tumor tissue. The fifth thoracic vertebra was the seat of tumor tissue replacing the bone. The right suprarenal gland was smaller than normal. The left suprarenal gland was replaced by a large mass, 9.5 by 9.5 by 5 cm. The tumor apparently arising from the suprarenal gland had destroyed it and had metastasized without invading the kidney. On section, the primary tumor was an opaque gray with yellow areas. It did not resemble the usual hypernephroma. The metastatic nodules resembled the original tumor in structure.

The sections studied were taken from the primary mass in the suprarenal gland, which was largely necrotic, and from one of the metastatic nodules in the liver. The primary tumor showed necrosis and degeneration at the center of the specimen, but the metastases showed a more cellular and diffusely growing neoplasm. The malignant characteristics of diffuse carcinoma of the suprarenal cortex were evident in both sections. The nuclei were prominent and hyperchromatic and contained many mitotic figures. The cytoplasm was small in amount and formed a small ring about the nucleus. The cells grew in sheets or in lobulated masses separated here and there by a small amount of stroma.

2. Dr. W. T. Longcope, Professor of Medicine, Johns Hopkins University, gave permission to include this case studied in the medical wards.

MEDULLARY TUMORS

Tumors of the suprarenal medulla arise from the chromaffin cells of this organ or from cells of the sympathetic nervous system. The earliest forms of the sympathetic neural elements represent the common

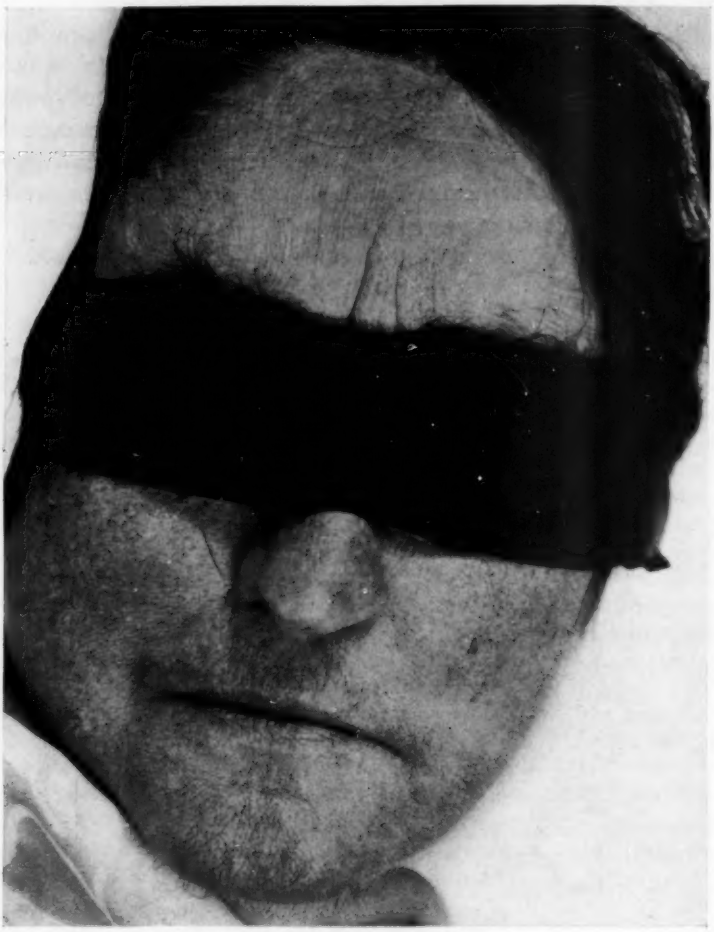

Fig. 2.—Appearance of the patient with the cortical carcinoma of the suprarenal gland shown in figure 1*B*. The patient was 57 years of age and complained of weakness. She had edema about the hands and ankles and marked virilism, as indicated by the growth of hair on the upper lip and chin seen in the photograph. The blood pressure was 190 systolic and 88 diastolic. The tumor metastasized to the liver and bones without invading the neighboring kidney.

ancestors for both the adult chromaffin tissue and the adult sympathetic tissue found within the suprarenal gland. Thus, while there is a distinction between the more highly differentiated ganglionic tumors and

tumors of chromaffin tissue, the more undifferentiated sympathetic nerve tumors are common to both the suprarenal medulla and the sympathetic nerve tissue wherever it occurs in the body.

Chromaffin Cell Carcinomas and Pheochromocytomas or Paragangliomas.—Tumors of the chromaffin cells of the suprarenal medulla are perhaps the rarest of the neoplasms involving this organ. They occur uniformly in adults and are usually accidental findings at autopsy. The growths are small and encapsulated. They are a mottled suprarenal color (yellow-brown-red). They may be bilateral. These tumors may be divided into benign and malignant forms.

In the malignant chromaffin cell carcinomas the cells are large and epithelial-like, grow in alveolar-like arrangement or in sheets, and show many bizarre nuclear forms and tumor giant cells. Some of the diagnostic criteria of these tumors are—absence of fat, lipoids and glycogen in the cells, a positive chromate reaction, and the large, malignant, epithelial-like cells forming syncytial masses or tumor giant cells. The case reported in the following paragraphs is illustrative:

A white man, 40 years of age, who appeared to be in good health, suddenly began vomiting. This continued for the greater part of the night. He was admitted to a hospital the following morning in a state of complete collapse. He was given hypodermoclysis and the routine treatment for shock, but in spite of this he expired three hours after admission. Laboratory findings showed a hemoglobin content of 90 per cent, 7,300,000 red blood cells and 23,000 white blood cells.

At autopsy, antimony was recovered from the corroded surfaces of the gastric and duodenal mucosa. A tumor the size of a small orange was found at the upper pole of the left kidney completely obliterating any evidence of the left suprarenal gland. This mass was smooth, encapsulated and easily shelled from the retroperitoneal fat.

The section (fig. 3 *A*) showed a malignant tumor of the suprarenal medulla, a so-called chromaffin cell carcinoma. There were many large dilated blood spaces filled with hemorrhage. About these spaces were scattered chromaffin and blood pigment. The tumor cells were large and epithelial-like, containing one or more large nuclei with many degenerating and bizarre forms. The cytoplasm was large in amount and not definitely demarcated. The resemblance of these cells to the ganglionic type was marked, but combined degenerating forms were more numerous.

The benign paragangliomas are chromaffin tumors which resemble the normal cells of the suprarenal medulla, but less markedly than the chromaffin carcinomas. They are more frequent outside of the suprarenal gland and are best represented by tumors of the carotid body and the carcinoids of the gastro-intestinal tract. The rare malignant paragangliomas of the suprarenal gland that have been described resemble more closely ganglionic sarcoma and show a neurogenic rather than a chromaffin character. The benign tumors are usually confined to adult life, are often accidental findings at autopsy and are clinically

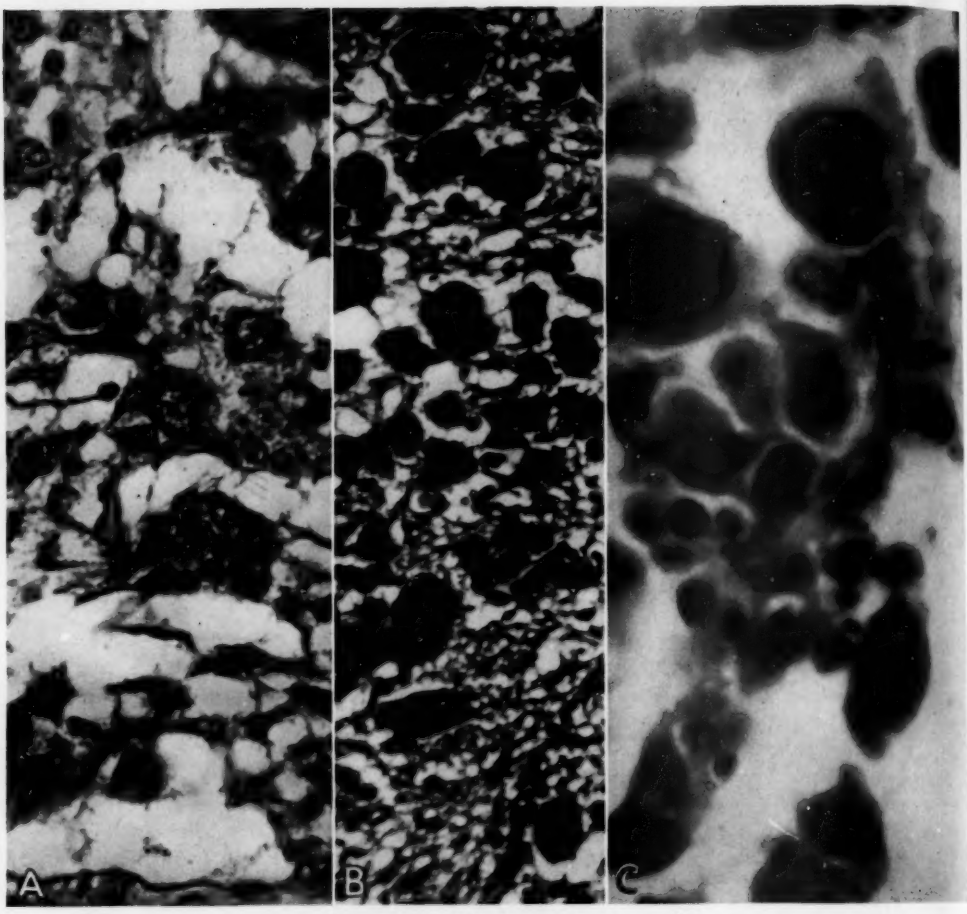

Fig. 3.—*A*, photomicrograph of chromaffin cell carcinoma of the suprarenal medulla. There are numerous giant cells of the tumor type, and the cytoplasm of the cells stains with hematoxylin. The patient was a white man, aged 40, who died of antimony poisoning. The tumor, which was the size of an orange, was found at the site of the left suprarenal gland at autopsy. It had given no symptoms during life, as far as could be determined from the history.

B, photomicrograph showing benign ganglioneuroma. The tumor was found in the retroperitoneal space near the suprarenal gland at autopsy. The enlarged ganglionic cells with small eccentric nuclei are embedded in a reticulated substance of nerve fibrils. This type of tumor, which is usually asymptomatic and benign, is not peculiar to the suprarenal gland; it may be found along the sympathetic nerve fibers accompanying the blood vessels anywhere in the body and also in the central nervous system.

C, high power photomicrograph showing ganglionic sarcoma of the suprarenal medulla. The tumor was found in a white woman, aged 55, with a tumor protruding from the socket of a tooth that had been extracted three weeks previously. She had enlargement of the cervical lymph nodes and a palpable mass above the right kidney. At autopsy, metastases were found extending to the bones and all the viscera. *C* shows the large malignant cells embedded in the suprarenal medulla. Ganglionic sarcoma containing these large malignant cells with degenerating cytoplasm, like benign ganglioneuroma, is not peculiar to the suprarenal gland and may occur in any of the outlying ganglions of the sympathetic nervous system. (Section through the courtesy of Dr. Wallerstein.)

associated with hypertension, vasomotor instability, glycosuria and in some instances a multiple neurofibromatosis or von Recklinghausen's disease. The tumors are inclined to have an alveolar arrangement; the cells have moderate dimensions with a medium-sized nucleus and a moderate amount of cytoplasm. The same tendency for a syncytial mass seen in the chromaffin carcinomas is manifest in these growths (fig. 5 *A*).

Ganglioneuromas and Ganglionic Sarcoma.—Differentiated neurogenic tissue of the suprarenal medulla may give rise to fairly mature ganglionic cell tumors. These tumors may be either benign or malignant. They are equally rare in the suprarenal gland and other sympathetic structures. Cases of malignancy in this group have been recorded more frequently in recent years.

The usual benign ganglioneuroma is a small tumor found accidentally at autopsy within the medullary substance of the suprarenal gland or occasionally overlying this gland and arising from sympathetic structures at the hilus. Such tumors are composed of a mass of fibrils enclosing occasional large ganglionic cells (fig. 3 *B*). Less differentiated tumors of this group show an increasing number of poorly developed ganglionic cells and local invasiveness and may give rise to definite metastases (fig. 3 *C*).

This entire group of ganglionic tumors is met with in sympathetic structures other than the suprarenal glands. However, ganglionic tumors of malignant nature are rarely recognized as such. If they are found in the region of the suprarenal gland, they are sometimes loosely referred to as hypernephromas, although they have nothing in common with the usual group of renal tumors incorrectly known by that name. When occurring in other organs, such as the thyroid gland, breast or soft parts, they are often mistaken for xanthosarcoma. Their structures indicate an origin from the outlying sympathetic ganglions or from the less constant ganglions which occur along the sympathetic fibers accompanying blood vessels throughout the body. In these normal outlying ganglions can be found the reticulated and fibrillated stroma and the large ganglionic cells which are always components of this group of tumors whether they assume the more benign slowly growing form of ganglioneuroma or the more rapidly growing malignant form of ganglionic sarcoma.

Malignant ganglionic tumors of the suprarenal medulla composed of large cells with eccentric nuclei are difficult to distinguish at times from chromaffin carcinomas arising in the same location. They have been incorrectly classed as malignant paragangliomas. The chromaffin tumors are also prone to produce large cells with eccentric nuclei and tumor giant cells. Chromaffin carcinomas, however, are less malignant in appearance. The latter may be differentiated from ganglioneuromas by

their chromate reaction, by the absence of the fibrillar stroma and by the staining of their cytoplasm with hematoxylin when the staining of the section is slow and prolonged.

Neuroblastomas Including Sympathoblastoma and Sympathetic Neuroblastomas.—Two varieties of undifferentiated sympathetic nerve tumors are found in the suprarenal gland. Both of these are commonly referred to under the general name of neuroblastoma and sometimes under the term of neurocytoma. The more undifferentiated tumors are composed of extremely small round cells with small fibrillae and a minimum amount of cytoplasm and are confined almost exclusively to late fetal life or early infancy. The more differentiated tumors are composed of spindle cells or larger round cells with a small but definite amount of cytoplasm. Tumors of the latter type, which have been variously labeled, are midway in differentiation between the small cell sympathoblastomas and the larger cell ganglionic tumors and paragangliomas that have been described (fig. 3). They usually occur in adults beyond the age of 45. In this paper they are referred to as sympathetic neuroblastoma, the term sympathoblastoma or neuroblastoma being reserved for the more undifferentiated tumors of infancy.

Among the neuroblastomas a clinical division was formerly made between tumors of the so-called Pepper type and those of the Hutchinson type. Growths characterized clinically by metastases to the liver were referred to as the Pepper type, whereas those in which bony metastases to the skull were a prominent clinical feature were referred to as the Hutchinson type. Neuroblastomas in which extreme involvement of the bone marrow with symptoms simulating pernicious anemia occurred have been designated in the literature as the Esser-Herwig type. These clinical classifications are pathologically misleading, as it has been recently shown that the various manifestations caused by the metastatic predilections for certain regions are dependent neither on the cell type nor on the relation of the primary tumor to the neighboring lymph or blood vessels but rather to the age of the patient.

The sympathoblastomas, that is, the undifferentiated small cell tumors, are confined almost exclusively to late fetal life or earliest infancy. They are extremely malignant, invading the retroperitoneal lymph nodes and metastasizing to the liver, lungs and bones. They may occur in both suprarenal glands and may replace these structures with large, soft growths of mottled yellow-brown color.

Their microscopic structure is fairly uniform and is characteristic. Many nests of small round cells are separated by a network of fibrillated stroma. The cell masses are often arranged in fairly characteristic rosettes (fig. 4 *A* and *B*). The cell, though small, has a faint refractile rim of cytoplasm, and the nucleus, which predominates, is dense, but often shows vacuolated, degenerating forms. It was this group of

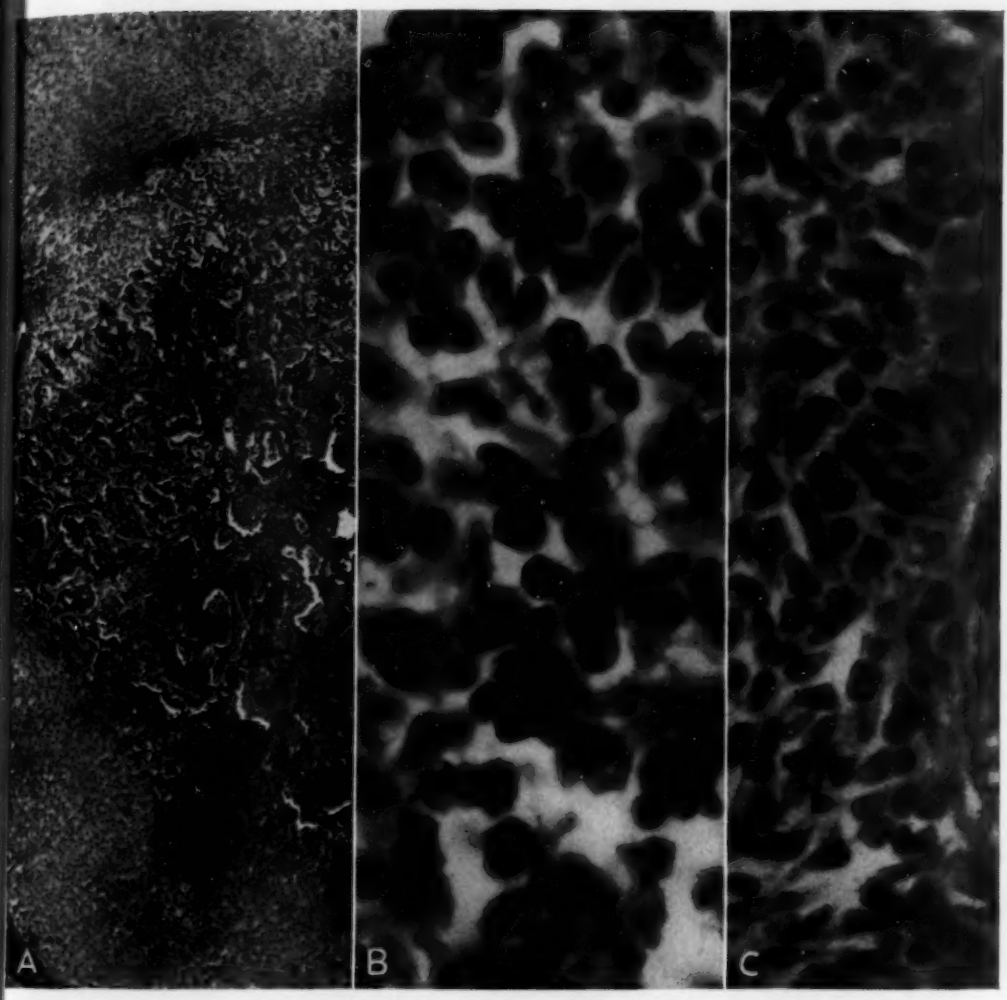

Fig. 4.—*A*, low power photomicrograph of so-called sympathoblastoma or neuroblastoma of the suprarenal medulla. This type of tumor tends to metastasize to the liver or to the bones and is usually found in infants. A tumor microscopically identical is known as retinoblastoma and may be found invading the eye and orbit of young children.

B, high power photomicrograph of sympathoblastoma (sometimes referred to as neurocytoma or sympathogonioma) of the suprarenal medulla. The tumor occurred in a full term fetus with a large abdominal mass which prevented normal delivery. The liver at autopsy weighed 700 Gm. and was studded with white nodules. The right suprarenal gland was replaced by a tumor, 6 cm. in diameter, which had attached itself to the pole of the right kidney. The cells of the tumor have little cytoplasm and are often mistaken for lymphocytes. This type of tumor was originally described as a form of lymphosarcoma. The reticulated stroma and the formation of rosettes are distinguishing characteristics.

C, photomicrograph of so-called sympathetic neuroblastoma of the suprarenal medulla. This tumor is midway in differentiation between the sympathoblastoma and paraganglioma. It was found in a white man, 45 years of age, whose first symptoms were those of backache simulating sacro-iliac strain. X-ray pictures of the spine showed pathologic fracture of the fourth lumbar vertebra. A metastatic tumor mass developed in the left axilla. At autopsy, the tumor involved the bones, brain, lungs, lymph nodes and suprarenal glands. The cells vary in type from small neuroblasts with occasional rosette formation, to cells approaching the ganglionic cell in appearance. The spindle cells seen in the photograph predominated in the tumor as a whole.

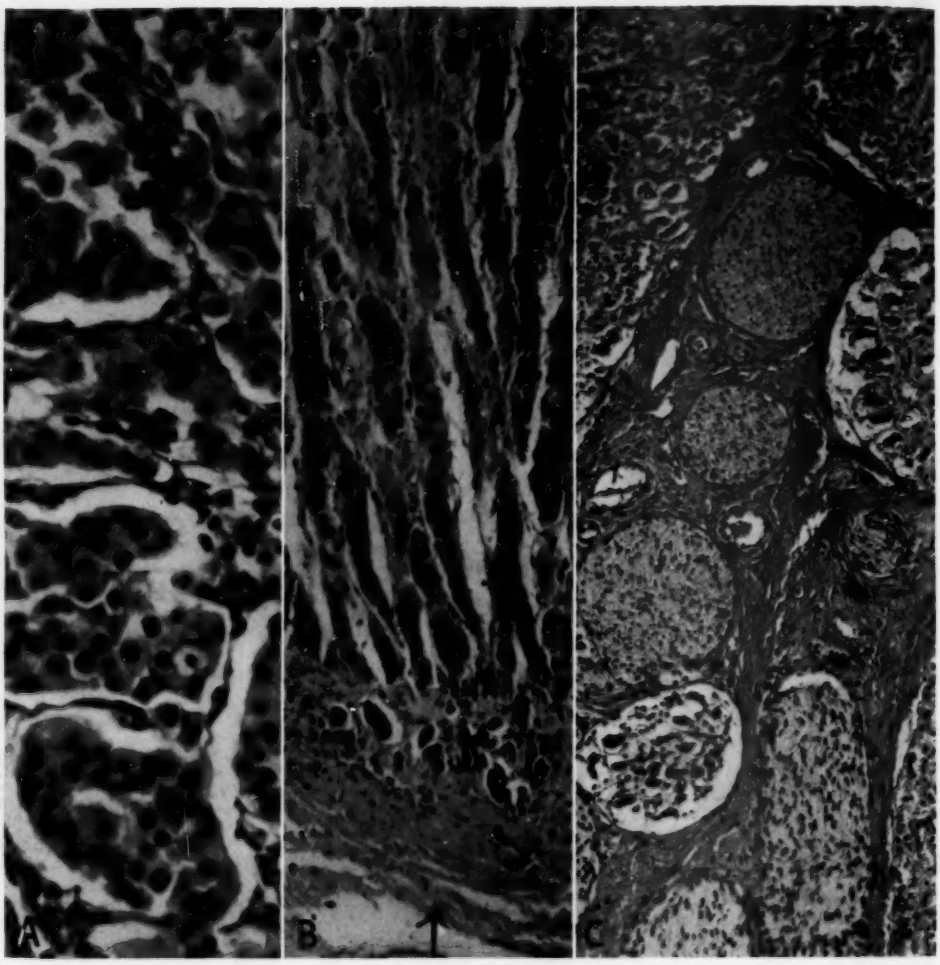

Fig. 5.—*A*, photomicrograph of a paraganglioma of the suprarenal medulla. The tumor occurred in a white woman, 53 years of age, with symptoms referable to the urinary tract. A pyelogram showed the tumor to be displacing the left kidney, and at operation a cystic mass the size of a grapefruit was found in the position of the left suprarenal gland. There was no recurrence one and a half years after operation. The tumor with its cell nests marked off by thin fibrous strands resembles the tumors of the carotid body. There are occasional mitotic figures and hyperchromatic nuclei and a prominent amount of cytoplasm.

B, photomicrograph of normal suprarenal cortex showing small islands of undifferentiated mesothelial cells which may give rise to cortical carcinomas of the suprarenal gland.

C, photomicrograph of a section of a nerve entering the suprarenal medulla and containing nests of ganglionic cells. Among these ganglionic cells are small, undifferentiated neuroblasts. Some of the more differentiated tumors of the suprarenal gland may arise from these outlying sympathetic ganglions.

tumors which was formerly erroneously classed with the lymphosarcomas. Forms of these tumors have been described which contain bulky masses of glial fibrils.[3]

The better differentiated sympathetic neuroblastomas may remain relatively small, without marked local invasiveness, and yet give rise to extensive metastases. Microscopically, the cells vary from the small undifferentiated cells of neuroblastomas with or without the formation of rosettes and glia-like stroma, to spindle cell shapes and thence to large ganglionic types (fig. 4 *C*). These spindle cells often have a wedge or carrot-like shape, and by some authors are regarded as spongioblasts. The wide variation of cell forms has led to confusion of this type of tumor with the adenomyosarcoma of the kidney (Wilms' tumor). However, on careful examination, the small cells arranged in rosettes,

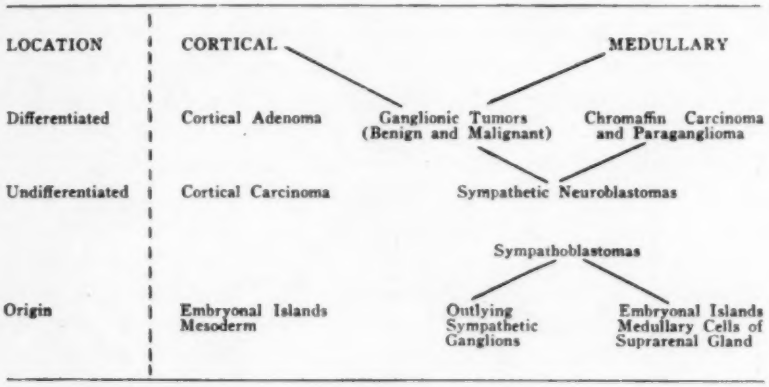

Fig. 6.—Outline showing relationships of tumors discussed in this paper.

the glial-like fibrils, the ganglionic giant cells and the absence of tubule formation or of myomatous structures should aid in making the distinction.

HISTOGENESIS

A review of the pathology of suprarenal tumors makes it possible for the classification of new growths in this region to be greatly simplified. The cortical tumors of the suprarenal glands arise from small islands of undifferentiated mesenchymal tissue related in origin to the sex glands. These small embryonal islands can be found in normal suprarenal glands in the region of the capsule (fig. 5 *B*). When slowly proliferating, these cells give rise to the benign cortical adenomas without marked clinical symptoms; when more rapidly proliferating, they

3. Ewing, James: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

give rise to cortical carcinomas with clinical changes in the sexual characteristics of the patient.

The medullary tumors of the suprarenal glands are of the nature either of sympathetic nerve tissue or of chromaffin tissue, both of which have a common origin in undifferentiated neurogenic tissue of the sympathetic type. The more slowly growing sympathetic nerve tumors give rise to ganglioneuromas or ganglionic sarcoma. The chromaffin tissue gives rise to chromaffin cell carcinoma and to paragangliomas. The more undifferentiated neurogenic tissue gives rise in childhood to the malignant sympathoblastomas and in adult life to the malignant sympathetic neuroblastomas. The neurogenic tumors may arise from undifferentiated cells of the suprarenal medulla or from outlying ganglions of the sympathetic nerves which supply this organ (fig. 5 *C*). The relation of these tumors is indicated in the accompanying outline.

METHODS FOR MICROCHEMICAL DEMONSTRATION OF ARSENIC IN TISSUES

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AND
KATHLEEN B. MUIR, M.D.
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In 1905, Justus [1] introduced a method for microchemical demonstration of arsenic in tissue. Working with white mice poisoned with sodium arsenite injected subcutaneously, he first fixed the various organs in a 4 per cent formaldehyde solution. After being washed in water, the tissues, cut into thin sections, were placed in a saturated solution of hydrogen sulphide for several days at about 70 C. They were then washed, carried through increasing concentrations of alcohol and ether, embedded in pyroxylin, cut, treated for a short time in hydrochloric acid (dilute), stained and mounted. When studied microscopically, the sections were seen to contain small highly refractile, greenish-yellow, round and elongated crystals. These, Justus stated, were crystals of arsenic trisulphide, produced by the action of hydrogen sulphide on the arsenic in the tissues. He stated that a part of the arsenic in tissue is present as arsenate, while another portion, in all probability, is present in some combination with the tissue. The passing of hydrogen sulphide gas through a solution of sodium arsenate in vitro produced a colloidal suspension of arsenic trisulphide which could be precipitated by acids or alkalis or by allowing it to stand for a long period at relatively high temperatures. Justus did not mention what he found in normal animals whose tissues were treated by this method.

Brünauer,[2] in 1921, reported the results of his study of a case of arsenical hyperkeratosis in a patient who had taken a solution of potassium arsenite (Fowler's solution) for a considerable time. Using a slight modification of Justus' hydrogen sulphide method, he treated some of the hyperkeratotic tissue and found the small yellow crystals described by Justus. His control was a section of nonarsenical keratoderma palmare, in which he found none of the brown granules. He did not mention the results obtained when normal tissue was treated by this method.

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This work was performed in part during tenure of a fellowship in the Douglas Smith Foundation of the University of Chicago.

1. Justus, J.: Dermat. Ztschr. **12**:277, 1905.
2. Brünauer, S. R.: Arch. f. Dermat. u. Syph. **129**:186, 1921

In 1925, Osborne [3] reported his findings in the study of arsenical pigmentation and keratosis, using Brünauer's modification of Justus' method. He stated that normal human and rabbit's skin was examined for arsenic by the same method, with negative results. Osborne later [4] used this method in his study of arsenical dermatitis, and again [5] in microchemical studies following the administration of arsphenamines and tryparsamide. Using Osborne's method, Memmesheimer [6] demonstrated crystals of arsenic trisulphide in cases of lichenoid arsphenamine dermatitis, and failed to find them in one case of exfoliative arsphenamine dermatitis and in one case of urticaria following the use of arsphenamine. He did not mention his findings in normal controls.

During a study on the reaction of the reticulo-endothelial system to drugs used in the treatment of syphilis, one of us (K. B. M.) noted that while foreign material was present in sections treated with hydrogen sulphide, the same material seemed to be present in the controls. To verify this finding, using Osborne's method, we studied tissues from both normal animals and animals that had received lethal doses of neoarsphenamine intravenously (rabbits) and of sodium arsenite and sodium cacodylate subcutaneously (white rats).

METHOD

Arsenic-free reagents must be used. The tissues were treated as follows:

1. Fixed in a dilute solution of formaldehyde, U. S. P., (1:10) for from twenty-four to forty-eight hours.

2. Washed in running tap water for twenty-four hours.

3. Cut into small pieces about 2 mm. thick.

4. Put in a 1 ounce (30 cc.) ground glass, glass-stoppered bottle, which was nearly filled with fresh neutral hydrogen sulphide solution. (A small amount of petrolatum was placed on the stopper which was inserted tightly and bound down with adhesive tape. The bottle was then placed in an incubator at 70 C. for four days, fresh hydrogen sulphide being added each day. We found that it was much more satisfactory to put the saturated hydrogen sulphide solution and tissues into pyrex test tubes, the ends of which were then sealed in an oxygen flame. This obviated any loss of hydrogen sulphide from loose stoppers. The latter part of the work was done in this way.)

5. Washed in running water for twenty-four hours.

6. Dehydrated in 50, 70, 80 and 95 per cent absolute alcohols, each solution containing about 10 per cent of ether.

7. Embedded in pyroxylin and cut into sections about 5 microns in thickness.

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3. Osborne, Earl D.: Arch. Dermat. & Syph. **12**:773, 1925.

4. Osborne, Earl D.: Arch. Dermat. & Syph. **18**:37, 1928.

5. Osborne, Earl D.; Putnam, Edwin D., and Hitchcock, Blanche S.: Arch. Dermat. & Syph. **25**:419, 1932.

6. Memmesheimer, A. M.: Dermat. Ztschr. **54**:4, 1928.

8. Placed for twenty minutes in 10 per cent hydrochloric acid in alcohol in order to remove all sulphides except arsenic trisulphide.

9. Washed for twenty minutes in 70 per cent alcohol, and stained with hematoxylin and eosin.

10. Differentiated in 95 per cent alcohol.

11. Cleared in oil of cloves, and excess removed with xylene.

12. Mounted in Canada balsam.

The sections from both the normal and the poisoned animals showed the same round and elongated, greenish-yellow, highly refractile crystals mentioned by Justus, Brünauer and Osborne. In all the sections the crystals exhibited the same peculiarities of refraction described by Osborne—a solid mass with a bright halo when in focus; a clear center and a heavy rim with a slight halo when too near the objective, and a clear center and a faint rim with little or no halo when beyond the focus. That the precipitate in all sections (normal and poisoned animals) was made up of true crystals was verified by examination with the polarizing microscope.

It was at first thought that, since they were found in the controls, these crystals might be produced in some way by the pyroxylin embedding, that they might be artefacts. The same procedure was carried out again, the specimens being embedded in paraffin instead of pyroxlin. The results were identical with those obtained with pyroxylin.

The reasons given by Osborne for utilizing the more tedious pyroxylin method is that the alcohol and ether and pyroxylin dissolve any precipitated sulphur that might be present. We could not see any difference in the sections prepared by the two methods. The xylene used in the paraffin method also dissolves sulphur.

In order to determine further what rôle heat played in the production of the crystals, the method was followed as before except that the tissues were kept at room temperature instead of being incubated for four days at 70 C. Microscopic examination revealed the crystals in all sections.

The possibility of the crystals being sulphur was next considered. Sulphur is very slowly soluble in alcohol, ether, pyroxylin and xylene. Carbon disulphide is the solvent par excellence for sulphur. The procedure was repeated, the tissues being treated for from two to four hours in an extractor with carbon disulphide just after they were run through the various alcohols. The crystalline precipitate was still present at the end.

In an attempt to find a solvent for these crystals, the following reagents were used: sodium hydroxide, sodium bicarbonate, sodium thiosulphate, potassium bisulphite, ammonium hydroxide, mercuric chloride, hydrochloric acid, sulphuric acid, nitric acid, acetic acid, potassium

oxalate, acetone, aniline and acid aniline. The crystals were insoluble in all of these reagents. This proved that they were not crystals of arsenic trisulphide, because the latter are readily soluble in sodium hydroxide.

It was decided to treat the tissues with hydrogen sulphide before fixation. Organs were removed from a normal animal and from an animal which had received a lethal dose of sodium arsenite. They were cut into thin sections and placed in a vacuum chamber; the air was exhausted and hydrogen sulphide introduced to saturation. The tissues quickly turned black and were allowed to remain in the chamber for about twelve hours, when they were removed, washed for a short time in running water and then divided into two parts. One part was fixed in a dilute solution of formaldehyde, U. S. P. (1 : 10) and the other in alcohol, and both were treated with dilute hydrochloric acid to remove sulphides other than arsenic trisulphide. All sections showed a heavy deposit of the crystals. Negative results were obtained when the sections were examined for iron by the potassium ferrocyanide-hydrochloric acid method.

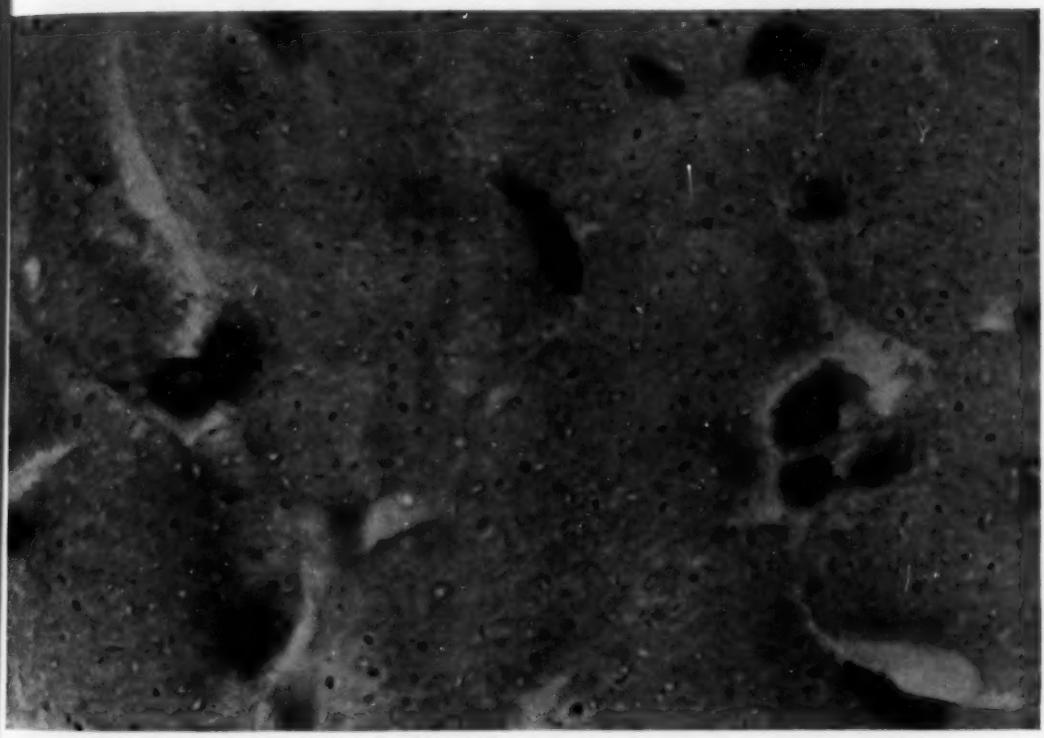
It was decided to ascertain whether crystals of arsenic trisulphide could be precipitated in a fixed protein (colloid) medium, and whether the presence of blood in any way influenced the formation of the crystals found in the sections. A concentrated solution of egg albumin was prepared. This was divided into four parts as follows: (1) solution of egg albumin; (2) solution of egg albumin plus solution of sodium arsenite; (3) solution of egg albumin plus red blood cells, and (4) solution of egg albumin plus blood serum.

An agar gel was then prepared, and while this was still at the boiling point it was divided into four parts and egg albumin solutions 1, 2, 3 and 4 were added, the albumin coagulating immediately. When the preparations were cool, blocks were cut and treated with hydrogen sulphide just as the tissues had been. After embedding in paraffin, sections were cut and examined microscopically. In all four sections yellowish, highly refractile crystals were seen. These were present in greatest amount in the section containing the blood serum. If crystals of arsenic trisulphide were present in the sections which had contained the sodium arsenite solution, they were not distinguishable from the crystals found in the other sections.

In order to determine what influence blood had in the production of these crystals, two normal white rats were killed. The vessels leading to and from the heart of one rat were ligated; the organ was removed, fixed in a dilute solution of formaldehyde and treated by the hydrogen sulphide method described. The heart of the other animal was perfused with physiologic solution of sodium chloride until it was exsanguinated,

fixed in formaldehyde and treated by the same method. Crystals were found in the sections from both animals, although in the heart containing blood they were diffusely distributed and in the exsanguinated heart they were confined to the muscle cells (fig.).

It was found that if the tissues were treated with hydrogen sulphide in an acid medium before fixation, the profuse crystalline precipitate did not occur. However, one could not distinguish the sections of the normal animal from those of the animal that had received a lethal dose of sodium arsenite. Moreover, if the tissues were fixed in alcohol



Crystals in muscle of a normal exsanguinated heart (white rat) after fixation in formaldehyde and treatment with hydrogen sulphide. Hemalum and eosin counterstain; oil immersion preparation.

instead of in formaldehyde before being treated with hydrogen sulphide, the diffuse crystalline precipitate was not seen. But here also normal sections were practically identical with the sections from the poisoned animal.

COMMENT

From these experiments we conclude that the crystals formed during the hydrogen sulphide treatment of formaldehyde-fixed tissue containing arsenic have not been proved to be those of arsenic trisulphide.

The crystalline nature of the precipitate was proved by the polarizing microscope. Prolonged extraction with carbon disulphide, which readily dissolves crystalline sulphur, did not remove them. They were not dissolved by any of the common solvents, including sodium hydroxide, which would have dissolved arsenic trisulphide. Fixation of the tissue in alcohol before treatment with hydrogen sulphide prevented the formation of the crystals, although they were found in tissue treated while fresh with hydrogen sulphide and later fixed in alcohol or formaldehyde. Treatment of tissue in an acid medium with hydrogen sulphide was not followed by formation of the crystals, even with fixation in formaldehyde. Treatment of egg albumin produced the same crystals, which were seen in greater numbers when blood serum had been added. The presence of sodium arsenite made no difference in the nature or in the number of the crystals. In an exsanguinated rat heart the crystals were confined to muscle cells while in a heart containing blood they were more diffusely distributed. On the basis of this, the crystals should be found in tissue containing more serum, such as that involved in inflammation. This could account for Osborne's finding of the crystals in the perivascular region in sections of exfoliative dermatitis due to arsphenamine. Anderson [7] found a few crystals of arsenic trisulphide in normal skin, but definitely more in a carcinomatous lesion, in which inflammatory changes are always present.

As to the chemical composition of these crystals, we believe that they are a sulphur-protein combination, since it is rather unlikely that arsenic trisulphide present in colloidal suspension in neutral solution would be precipitated in crystalline form in such a fixed colloidal system as is present in tissues.

In the hope that some other method might be evolved for the demonstration of arsenic in tissues, the following processes were tried: Since the silver salts of arsenous acid form bright yellow precipitates, an attempt was made to demonstrate arsenic in tissues by treatment with silver nitrate. Tissues were treated (in the dark) with silver nitrate solution, both before and after fixation. The results were not conclusive, as sections from the normal animal could not be distinguished from those obtained from the animal receiving a lethal dose of sodium arsenite. The colorimetric method for the demonstration of arsenic and phosphorus introduced by Denigès [8] and later modified by Truog and Meyer [9] was found unsatisfactory for the study of tissue because of the presence of large amounts of phosphorus and iron.

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7. Anderson, N. P.: Arch. Dermat. & Syph. **26**:1052, 1932.

8. Denigès, G.: Chem. Zentralbl. **2**:339, 1921.

9. Truog, Emil, and Meyer, A. H.: Indust. & Engin. Chem. (Analyt. Ed.) **1**:136, 1929.

SUMMARY

The literature relative to the demonstration of arsenic by means of hydrogen sulphide in tissues fixed in formaldehyde is discussed. In experimental work it was noted that control sections showed the same crystals as sections containing arsenic. The crystals were proved to be such by the polarizing microscope. They were not soluble in other solvents, including sodium hydroxide, so that they were evidently not arsenic trisulphide as had been supposed. Treatment of egg albumin alone and of egg albumin containing sodium arsenite, red blood cells and blood serum, respectively, with hydrogen sulphide, produced the same crystals in greater numbers in the material containing blood serum. An exsanguinated heart showed the crystals only in the muscle cells, while in a heart containing blood they were present throughout. Treatment of the tissue with hydrogen sulphide in an acid medium before fixation did not produce the crystals. Alcoholic fixation before treatment with hydrogen sulphide also was not followed by production of the crystals. In the latter two experiments, normal sections were identical with those containing arsenic. We believe that the crystals are a sulphur-protein combination and that they have not yet been proved to be crystals of arsenic trisulphide.

RAT CARCINOMA AND INJECTED COLLOIDAL PLATINUM

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In an earlier study (Guyer and Daniels,[1] 1928) on the irradiation of cancer in rats with cathode rays derived from a Coolidge tube, colloidal platinum was used as an internal target in certain experiments to determine whether possibly rays given off when the electrons struck colloidal metal particles within tumors were more effective than rays reflected from an external source. In the control animals given injections of colloidal platinum and left unirradiated, it was found that apparently a considerably greater percentage of "cures" occurred than in rats in which tumors had been implanted and which had been kept as controls in various other experiments. In rats of the latter type the percentage of spontaneous recoveries through healing or shrinking and ultimate disappearance was found to be about 8 (24 of 312 rats in which the transplanted tumors had become well established), whereas in a small group of animals into which platinum had been injected the percentage of recoveries was nearly 60 (7 of 12 in one experiment and 6 of 10 in another). Such a result obviously suggested further experimentation with platinum, and the present paper is a report on the results of such a study.

The cancer used was the Flexner-Jobling carcinoma. It was obtained from the Crocker Institute in the spring of 1926, and has since been kept in our laboratory through transplantation of small pieces from rat to rat. When once transplanted the cancer usually persists and grows, eventually causing the death of the animal. The percentage of "takes" in our stock has been consistently high. Thus, in an earlier study (Guyer and Daniels,[1] 1928) of 1,114 rats into which transplants were made, nearly 90 per cent showed development of tumors (993 did; 121 did not). In another series of 50 males and 52 females receiving transplants, all of the males (100 per cent) and 41 of the females (nearly 80 per cent) acquired tumors. In the present study based on rats which included none of the descendants of cured animals or of

From the Department of Zoology, the University of Wisconsin.

These investigations were supported by a research grant from Mary C. Brittingham.

1. Guyer, M. F., and Daniels, F.: J. Cancer Research **12**:2, 1928.

animals which had previously proved to be immune, of 762 in which cancer was implanted, 653 (85.7 per cent) showed well established "takes" with noticeable growth by the third week.

The rats used in the present investigation were from the Sprague-Dawley colony, which was also the source of the stock employed in the experiments with cathode rays already alluded to (Guyer and Daniels,[1] 1928), and of those used in a later study on cellular changes in the anterior lobe of the pituitary gland following transplantation of cancer (Guyer and Claus,[2] 1932). Young animals weighing between 60 and 80 Gm. were usually selected to receive the transplants. Series of control rats of the same age and ancestry were used in all experiments, and unless otherwise specified the distribution of males and females was about equal.

EXPERIMENTS WITH INTRATUMORAL INJECTIONS OF COLLOIDAL PLATINUM

In order to test further the inhibitive or curative effects of colloidal platinum on the Flexner-Jobling carcinoma, a series of five experiments, involving 342 rats in all, was undertaken. The colloidal suspension of platinum was prepared by sparking platinum electrodes in distilled water. The operation was continued until the metallic platinum began to settle out in the bottom of the container. Analysis of several samples showed an average of 17.3 mg. of platinum to each 100 cc. of the suspension.

The intratumoral injections were begun when the cancers were about 3 weeks old, when they averaged from 1.1 to 1.2 cm. in diameter. All tumors employed in the experiments approximated this average size. In selecting animals, an attempt was made to have the injected and the control cancers of equal dimensions.

The amount of colloidal platinum injected was as a rule about 0.15 cc. at the beginning of the injections. The amount was then varied correspondingly as the tumors increased or decreased in size. For example, a tumor 3 cm. in diameter would be given 0.3 cc., while a tumor 0.6 cm. in diameter would receive only 0.05 cc.

Injections were given every forty-eight hours. The number given at one time again varied with the size of the tumor. On an average, three injections into different parts of the tumor were given at the start. Particular care was taken to make the injections into the base. No attempt was made to make an injection into every part of the tumor at each treatment, but the site of injection was changed on successive days so that eventually the greater part of the tumor received injections.

The controls were not treated except in experiment 4, in which physiologic solution of sodium chloride was injected into the tumors. The injections of saline solution were made in the same manner as the injections of platinum, in order to simulate the mechanical injury caused by the latter.

Each tumor was measured weekly with calipers, and the diameter was recorded. If the tumor was oval the greatest and least dimensions were taken. Also, it was noted in our records whether the tumor was ulcerated or contracted to a scablike growth.

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2. Guyer, M. F., and Claus, P. E.: Anat. Rec. **52**:3, 1932.

Metastases to the axillae and inguinal regions were measured. Autopsies were made, and macroscopic metastases in the lungs, mediastinal lymph nodes, intestinal lymph nodes, pancreas, splenic capsule and other tissues were noted.

Table 1 summarizes the amount of healing in the 5 experiments as compared with the controls.

The graphs in figure 1 illustrate the percentage of healing in experiment 3, which was the most extensive and most accurate of the experiments. Figure 2 shows the rates of growth in the tumors into which platinum was injected and in the control tumors, respectively. Retardation in the growth of the tumors given injections is evident at a glance. That the colloidal platinum not only retards the growth of the tumor but temporarily prolongs the lives of rats so treated which eventually die is indicated by the graphs in figure 3.

In experiment 4 (table 1) physiologic solution of sodium chloride was injected into the tumors of the rats used as controls in order to see whether some of the inhibitory effect on the growth of the tumor might be due to the mechanical effects of the injection itself. That this may be the case is indicated by the rise in the percentage of healed tumors, although the number of animals used in the experiment is scarcely sufficient to warrant a positive conclusion. The 12 per cent difference between the tumors into which platinum was injected and those into which saline solution was injected, however, still leaves a sufficiently large margin to convince one that the colloidal platinum itself, apart from the mechanical disturbance incidental to its injection, has an inhibiting effect on the growth of cancer.

TABLE 1.—*Amount of Healing in the Respective Experiments*

		Rats That Received Injections			Controls			
Experiment	Number of Rats	Number Given Injections	Number Healed	Percentage Healed	Number Given Injections	Number Healed	Percentage Healed	Percentage Difference
1.....	73	50	7	14.0	23	1	4.3	+10
2.....	98	55	15	27.3	43	5	11.6	+16
3.....	108	68	34	50.0	40	8	20.0	+30
4.....	45	24	12	50.0	21	8	38.0	+12
5.....	18	9	2	22.0	9	0	0.0	+22
Total.....	342	206	70	34.0	136	22	13.0	+21

The time at which ulceration occurred was little if any later in the controls than in the tumors into which injections were made. Many of the latter regressed by absorption, no ulceration occurring. Moreover, some of these tumors grew to 3 or 4 cm. without ulcerating. The possibility that the regressions are due to earlier ulceration and sloughing caused by the injections is thus not an important factor. Ulceration and sloughing in any event produce only a temporary check in the increase of size due to the loss of the necrotic core of the tumor, the main part of the actively growing cancer being at the base of the tumor. The evidence indicates that ulceration is not necessarily linked with the healing process.

The experiments as a whole showed a marked tendency for the tumors into which platinum had been injected to regress. They healed in greater numbers than the control tumors; the healing was in general earlier, and the rate of growth of the tumors that did not heal was noticeably slowed, resulting in a longer life for the treated rats which eventually died of cancer than in the cancerous rats used as controls which died.

EXPERIMENTS WITH INTRATUMORAL INJECTIONS OF SILVER

For the purpose of control on the experiments with colloidal platinum it was decided, as experiment 6, to use colloidal suspensions of some other metal, and for this purpose silver was chosen. The same technic of intratumoral injection was used as that employed in the experiments with platinum. Forty rats were given

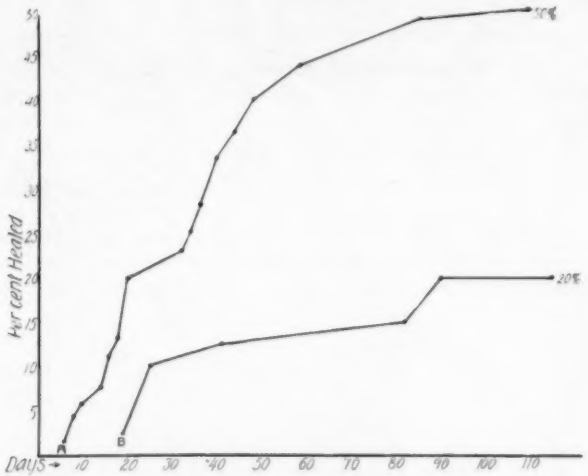

Fig. 1 (experiment 1, table 1).—Percentage of healing in rats given injections of colloidal platinum (*A*) and in those used as controls (*B*).

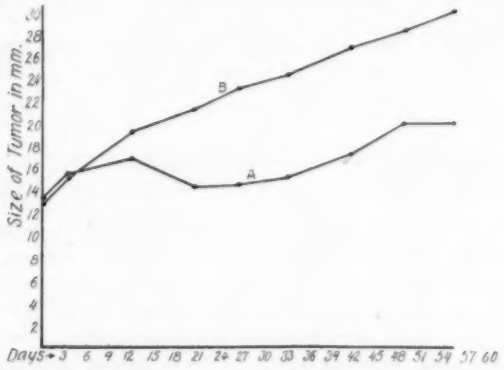

Fig. 2 (experiment 3, table 1).—Respective rates of growth of tumors in rats given injections of colloidal platinum (*A*) and in those used as controls (*B*).

injections, and thirty were used as controls. The tumors were all of an even size when treatment was begun, averaging about 1.3 cm. in diameter.

Of the 40 treated animals, only 1 (or 2.5 per cent) became healed and normal again. Of the 30 controls, 5 (or 16.6 per cent) became healed. In the rat that recovered, healing of the tumor into which silver had been injected required six weeks. The tumor measured 1.2 cm. in diameter at the beginning of treatment.

The initial sizes of the tumors in the 5 controls which eventually became healed were 1.2, 1.3, 1.3, 1.2, 1.2, 1.4 cm., respectively, and the average number of weeks required for the healing was six and six-tenths.

This experiment strongly indicates not only that intratumoral injections of colloidal silver do not inhibit the growth of cancer but that, on the contrary, they stimulate it. Moreover, the regressive effects which follow injections of colloidal platinum are, in the light of this experiment, due specifically to the colloidal platinum and are not merely the nonspecific result of an injected colloidal metal.

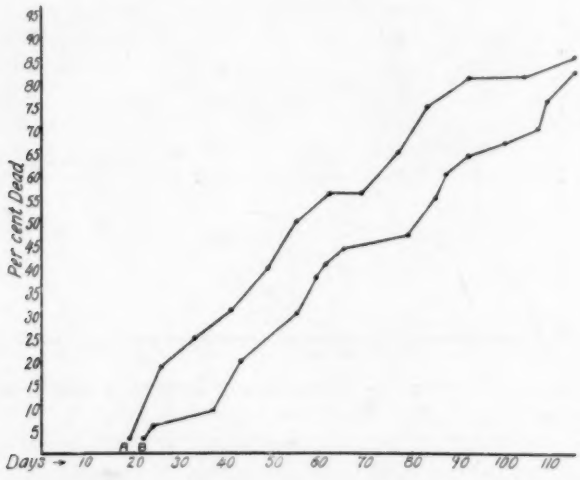

Fig. 3 (experiment 3, table 1).—Respective death rates of rats given injections of colloidal platinum (*B*) and of those used as controls (*A*), which died during experiment.

EXPERIMENTS WITH INJECTION OF COLLOIDAL PLATINUM COMBINED WITH TREATMENT BY ULTRAVIOLET RAYS

Earlier experiments (unpublished) indicated that mild irradiation with ultraviolet rays tended to inhibit the growth of transplanted tumors. It was decided to determine whether it is possible to combine these inhibitive properties with those of colloidal platinum. The rats used in the test were irradiated as a group at a distance of 30 inches (76.20 cm.) with ultraviolet rays from a mercury vapor, air-cooled lamp at a voltage of from 55 to 75, for a period of fifteen minutes every forty-eight hours, from a week before the cancers were planted to the end of the experiment.

In all of the rats, including those to be used as "platinum alone" controls, the tumor tissue was planted at the same time. Since there is likely to be some decrease in the viability of the cancer tissue after it has been outside the animal for a while and as different parts of the same piece of cancer may vary slightly in viability, the cancerous tissue was implanted alternately in rats of the two groups. This procedure also made for greater accuracy when it was necessary to use more than one tumor for implantation.

Injection of colloidal platinum intratumorally was begun twenty-eight days after the implantation of the tumors (thirty-three days afterward in experiment 7). When the injections were started, the average size of the tumors in experiment 7 was 1.4 cm., and in experiment 8, 0.8 cm. Both sets of rats were given injections of colloidal platinum every forty-eight hours in the usual manner.

The size of the tumors, the presence of ulceration and the occurrence of axillary metastases were recorded weekly. When the animals died autopsies were performed, and the presence of macroscopic metastases to the lungs and thorax was recorded (table 3).

Although experiment 7 was a preliminary one with only 16 rats, it is seen by the tables that the results check with those of experiment 8, in which 100 female rats were used.

From table 2 alone, which represents the end-results of the experiments, one might infer that the ultraviolet rays inhibit the curative effects of the colloidal

TABLE 2.—*Healing, Following Combined Treatment with Platinum and Ultraviolet Rays Compared with That Following Platinum Alone*

Experiment	Number of Rats	Rays and Platinum			Platinum Only		
		Number	Number Healed	Percentage Healed	Number	Number Healed	Percentage Healed
7.....	16	8	1	12.5	8	4	50
8.....	100	50	13	26	50	20	40

TABLE 3.—*Metastasis in Animals of Experiments 7 and 8*

Number of Autopsies		Percentage of Metastasis to Lungs		Percentage of Mediastinal Metastasis	
Rays and Platinum	Platinum	Rays and Platinum	Platinum	Rays and Platinum	Platinum
7	4	43	50	57	0
34	25	14.7	20	3	0

platinum. As seen in table 4, however, this antagonistic action does not appear significantly until after the tenth week of injection. Incidentally, this result checks with that obtained in another experiment with ultraviolet rays in which a marked spurt in healing of the unirradiated rats occurred late in the experiment. Possibly the ultraviolet rays hasten the healing of cancers that would heal spontaneously later anyway. Another suggestion that comes to mind is that an anticancer substance formed in the body due to the irradiation accumulates to a point where it stimulates the cancer instead of inhibiting it. Or, again, it does not seem improbable that the irradiation induces the formation of a lymphotoxin, small quantities of which stimulate the lymphoid system but larger quantities of which (or smaller quantities over a long period of time) injure the lymphoid elements, thus doing away with what may be one of the body's most potent defenses against cancer.

A result which favors the theory of an excess of lymphotoxin is seen in tables 3 and 4. There is a marked preponderance of metastasis to the mediastinal lymph nodes in the irradiated rats treated with platinum whereas in the rats treated with platinum alone the preponderance of metastasis was to the lungs. This indicates lymphoid injury which permits of more extensive metastasis in the mediastinal nodes of the rats irradiated over a long period of time.

TABLE 4.—*Data Found from Autopsies on Rats of Experiments 7 and 8*

	Weeks											
	1	2	3	4	5	6	7	8	9	10	11	12
Percentage healed												
Treatment with ultraviolet rays and colloidal platinum	2	12	16	16	16	16	18	18	22	24	28	26
Treatment with colloidal platinum alone	2	14	18	18	18	18	18	20	24	24	38	40
Difference	0	−2	−2	−2	−2	−2	0	−2	−2	0	−10	−14
Average size of tumors, cm.												
Treatment with ultraviolet rays and colloidal platinum	0.355	0.513	0.780	1.42	1.40	1.48	1.38	1.40	1.38	1.3	..	1.45
Treatment with colloidal platinum alone	0.324	0.514	0.84	1.54	1.62	1.60	1.45	1.29	1.33	1.3	..	1.5
Difference	−0.031	+0.001	+0.06	+0.12	+0.24	+0.12	+0.07	+0.11	+0.05	0	..	0.05
Percentage of cancers ulcerated												
Treatment with ultraviolet rays and colloidal platinum	.....	.....	0	21	89	100	100					
Treatment with colloidal platinum alone	.....	.....	7.3	37	69	100	100					
Difference	.....	.....	+7.3	+16	−20	0	0					
Percentage of axillary metastases												
Treatment with ultraviolet rays and colloidal platinum	.....	.....	.....	....	....	....	14	14	12	19	..	23
Treatment with colloidal platinum alone	.....	.....	.....	....	....	2	9	22	23	20	..	18
Difference	.....	.....	.....	....	....	+2	−5	+8	+11	+1	..	−5
Number of autopsies to date												
Treatment with ultraviolet rays and colloidal platinum	.....	.....	.....	....	....	....	....	1	1	3	4	35
Treatment with colloidal platinum alone	.....	.....	.....	....	....	....	....	....	2	3	3	25
Percentage with metastases to lungs												
Treatment with ultraviolet rays and colloidal platinum	.....	.....	.....	....	....	....	....	0	0	33	25	14
Treatment with colloidal platinum alone	.....	.....	.....	....	....	....	....	0	0	33	33	20
Difference	.....	.....	.....	....	....	....	....	0	0	0	+8	+6
Percentage with mediastinal metastases												
Treatment with ultraviolet rays and colloidal platinum	.....	.....	.....	....	....	....	....	0	0	33	25	3
Treatment with colloidal platinum alone	.....	.....	.....	....	....	....	....	0	0	0	0	0
Difference	.....	.....	.....	....	....	....	....	....	....	−33	−25	−3

The fact that the average size of the irradiated tumors into which platinum was injected was slightly smaller than that of the tumors into which platinum alone was injected throughout experiment 8, especially around the fifth week, is possibly significant. It will be noted that the difference in average size slowly rises to a peak at the fifth week, after which it gradually declines. This strongly suggests that the inhibiting effects of the rays were manifested in an increasing degree until the fifth week, after which they rapidly fell off. This in turn fits in with the idea of a lymphotoxic effect, the ultraviolet rays stimulating lymphoid resistance up to the fifth week, after which an overdose injures the resistance.

Little in the way of deductions regarding ulceration and axillary metastasis can be made from the tables. It appears that the irradiation delays ulceration for a few days.

In general, one apparently may legitimately conclude from the experiments that ultraviolet rays do not, permanently at least, augment the healing properties of colloidal platinum; that, in fact, they seem to inhibit these properties after the tenth week. Such rays appear to assist the colloidal platinum in retarding the growth of cancer up to the fifth week, after which their beneficial effects decline. Since there are indications that prolonged use of ultraviolet rays causes metastasis to the mediastinal lymph nodes rather than to the lungs, it does not seem improbable that these rays induce the formation of a lymphotoxin which for a period stimulates the lymphoid system to increased activity, but which eventually inhibits it owing either to stimulation for too long a period or possibly to a cumulative overdose. The inference would seem to be valid that the initial lymphoid stimulation caused an increased resistance to the cancers, whereas the eventual injury to the lymphoid system led to a diminished resistance.

HISTOLOGIC CHANGES INDUCED IN NORMAL AND IN CANCEROUS TISSUE BY INJECTIONS OF COLLOIDAL PLATINUM

In order to determine what histologic changes occur in cancers into which colloidal platinum has been injected, injections of this substance (experiment 9) were made into the right and the left sides of each of four tumors, and at intervals of one hour, four hours, twenty-four hours and forty-eight hours the sides of the tumors were removed, one side being cut parallel to the path of injection, and the other perpendicular to it. Likewise, 3 normal rats were given subcutaneous injections of colloidal platinum, and after intervals of one hour, four hours and twenty-four hours, respectively, a bit of the skin and the adjoining subcutaneous tissue was removed from the region in which the injection was made, and sections perpendicular to the surface of the skin were prepared for microscopic inspection. Some of the connective tissue was also spread on a slide and stained with Wright's stain to observe the cellular reaction.

Perhaps it is best to report first the result of injecting colloidal platinum into the subcutaneous tissue. After one hour and again after twenty-four hours the main visible reaction was a massive leukocytic infiltration around the particles of platinum (fig. 4, *1*). The latter seemed to have been largely precipitated by the tissue fluids. By the end of forty-eight hours, however, this infiltration was seen to have been almost wholly replaced by fibroblasts (fig. 4, *2* and *3*). Scat-

Explanation of Figure 4

1, subcutaneously injected colloidal platinum after twenty-four hours. A profuse leukocytic infiltration surrounds the deposited platinum (lower third of the section); × 60.

2, subcutaneously injected colloidal platinum after forty-eight hours. An extensive fibroblastic proliferation surrounds the deposited platinum (seen as a dark streak through the center of the section); × 60.

3, higher magnification (× 280) of section *2*. Fibroblasts and connective tissue fibrils are distinctly visible surrounding the treated area.

4, subcutaneously injected colloidal silver after ninety-six hours. The deposition of connective tissue is scanty, compared with that induced by colloidal platinum. The section reveals: (*a*) zone of silver deposit, characterized in the section by a yellow discoloration which does not appear in the photograph; (*b*) area of serous exudation with occasional fibroblasts; (*c*) striated muscle cells the cytoplasm of which is lysed; × 280.

5, section of the edge of an untreated tumor and the overlying skin, which is closely adherent; × 60.

6, section of the edge of a tumor: (*a*) colloidal platinum injected four hours previously; (*b*) marked leukocytic infiltration around the tumor tissue. The dark streak at the margin of the tumor is the deposited platinum; × 60.

7, section of the edge of a tumor: (*a*) colloidal platinum injected forty-eight hours previously; (*b*) marked fibroblastic proliferation around the tumor. The deposited platinum is seen as a dark streak at the edge of the tumor; × 60.

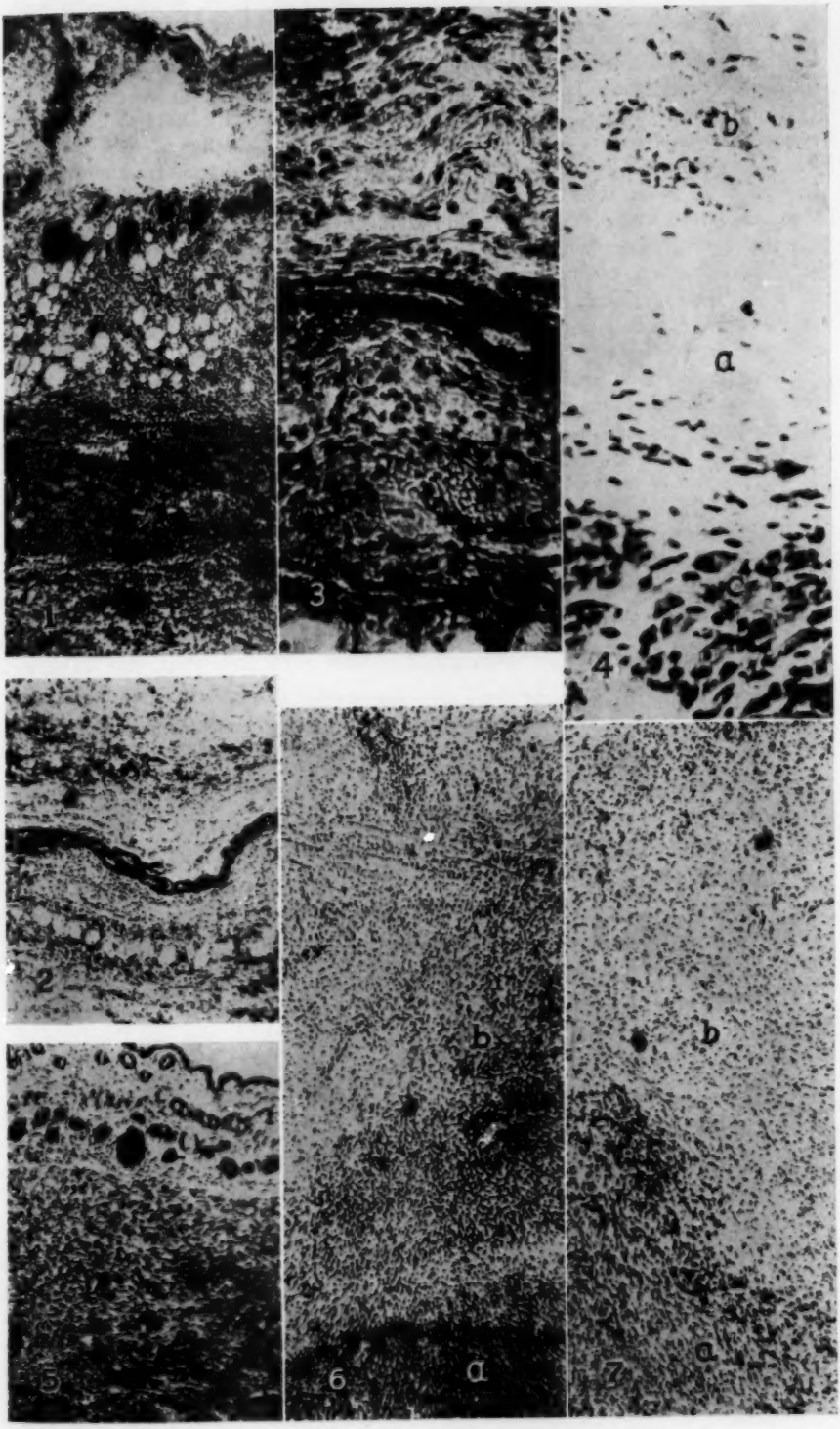

Figure 4

tered among the fibroblasts were numerous monocytes the cytoplasm of which contained minute particles of platinum.

In the cancer tissue the colloidal platinum caused much the same type of reaction, namely, first a leukocytic infiltration (fig. 4, *6*), followed in forty-eight hours by extensive fibroblastic proliferation (fig. 4, *7*). The leukocytic infiltration was about as great at the end of one hour as at the end of four hours. It was especially heavy along the paths of injection. Apparently along the needle's path, the tumor cells were lysed either by the platinum directly or by the leukocytes; at least, there was a considerable area along such paths from which the cancer cells had been displaced. Some of the cells bordering the path of injection had pyknotic nuclei, indicating recent necrosis. In some sections there were also indications of considerable subcutaneous exudation and hemorrhage.

After twenty-four hours, although the leukocytic infiltration was still manifest, fibroblastic proliferation was becoming marked. A peculiarly basophilic type of necrosis was seen in some of the cancer cells, and encapsulation of the tumor was obviously in progress.

By the end of forty-eight hours a thick capsule of fibroblasts had surrounded the tumor (fig. 4, *7*). Among these more typical connective tissue cells were scattered numerous phagocytes containing particles of platinum. The fibroblasts along the edge of the tumor were actively growing into the cancer tissue, and the cancer cells so surrounded were undergoing hydropic degeneration, possibly owing to the diminished supply of oxygen resulting from encapsulation.

The study of the sections all together indicates that the cancer-inhibiting properties of colloidal platinum are due either to the foreign body reaction elicited by the platinum or to a directly harmful action of platinum on cancer cells, or to both.

There can be no doubt that the platinum caused a marked foreign body reaction, whether injected subcutaneously or intratumorally. Cancer tissue, also, when implanted in normal tissue, doubtless incites a cellular and connective tissue reaction, but as the cancer usually grows and spreads, this reaction is of itself obviously inadequate. As already noted, platinum quickly induces a marked leukocytic infiltration. This infiltration is much more copious than that provoked by the cancer alone and may in itself be a potent factor in causing inhibition of cancer. Moreover, the marked fibroblastic proliferation which occurs within forty-eight hours after injection of the platinum would finally result in an ingrowth of the connective tissue and encapsulation of the tumor. The eventual contraction of this connective tissue capsule would probably result in pressure and anemia atrophy of the cancer tissue. If this is the mechanism which causes the inhibition of cancer, the colloidal platinum evidently has no direct effect on the cancer tissue; it merely acts by aiding the usual defense mechanisms of the body.

It may be, however, that the platinum is directly injurious to the cancer cells. If so, it is probably not operating by toxic action in the ordinary sense, since, even when massive doses are injected, it is not toxic to normal tissues or to the organism as a whole. On recalling the remarkable adsorptive property of colloidal platinum, one is prompted to

look into the possibility that it is causing some change in the metabolism of the cancer cells with which it is in contact. It might conceivably, through adsorption, be carrying into the tumor an excess of oxygen, or, on the contrary, adsorbing oxygen from the cancer tissues and the surrounding fluids, and thus causing death of the cancer cells through a deficiency of oxygen. The first possibility is dealt with experimentally in a later section. The second seems hardly tenable in view of the known fact that cancer cells can live in lower oxygen tensions than can normal tissues. Moreover, as shown in a later experiment (experiment 11), no very great direct effect of colloidal platinum on excised cancer was demonstrable. On the other hand, the lysis of the cancer cells and the pyknosis of their nuclei along the path of intratumoral injection suggest that some measure of direct effect cannot be ruled out.

It seems safe to conclude that the foreign body reaction induced by the intratumoral injection of colloidal platinum, which causes a rapid encapsulation of the tumor, is a fundamentally important factor in the inhibitions of growth and the cures which follow this treatment, but it is not clear that some direct action of the platinum on the cancer cells may not also be involved.

EFFECTS OF COLLOIDAL PLATINUM ON CANCER IN VITRO

An attempt was made to determine the effect of colloidal platinum on the cancer in vitro. Pieces of cancer tissue of the size ordinarily used for transplants were cut and placed in colloidal platinum. Similar bits of the tissue were placed in 0.7 per cent saline solution. By means of a warm stage both sets of preparations were kept at a temperature of 98.6 F. Pieces were removed from the colloidal platinum at intervals of ten minutes, thirty minutes and two hours, fixed and sectioned. The tissues in the saline solution were removed at the end of two hours and similarly fixed and sectioned.

The fragments immersed in colloidal platinum showed considerable hydropic degeneration, especially around the edges. This was also true, however, though possibly in a less degree, of the tissues immersed in the salt solution. The swelling in question corresponded to that seen in tumors into which platinum had been injected and some other tumors in vivo, probably a result of diminished oxidation. Some of the nuclei on the border of the fragments removed from the colloidal platinum solution had undergone pyknosis, but this was inconstant.

IMMERSION OF CANCER TISSUE IN COLLOIDAL PLATINUM BEFORE PLANTING

To determine the possibly harmful effect of immersing tumor tissue in colloidal platinum before implanting it in rats, ten fragments of cancer were placed in colloidal platinum for from ten to fifteen minutes; ten were similarly immersed in 0.7 per cent salt solution, and ten were transplanted directly to the animals. The fragments that had been immersed in colloidal platinum were dipped once in salt solution before implantation in order to remove particles of platinum. The 30 rats used were mature males from the laboratory stock. The results are shown in table 5.

While the outcome indicates some loss of the power of growth in the transplants due to immersion in colloidal platinum, the difference is not great. It is not impossible that notwithstanding the rinsing in salt solution particles of platinum may have clung to the fragments and induced a greater foreign body reaction similar to that which follows the intratumoral injection of platinum. In any event, immersion in colloidal platinum apparently causes but slight diminution in the virulence of the transplanted cancer.

In order to test the matter further and to introduce a slightly different control by using plain water, such as that present in the platinum suspension, instead of salt solution, a new series of tests was made. Fragments of tumor tissue were immersed for two hours in the colloidal platinum medium; other fragments were

TABLE 5.—*Effect on Transplants of Previous Immersion in Colloidal Platinum*

	Controls		Salt Solution		Colloidal Platinum	
Days	Average Size of Tumor, Cm.	Number Healed	Average Size of Tumor, Cm.	Number Healed	Average Size of Tumor, Cm.	Number Healed
9	0.22	0	0.26	1	0.20	0
15	0.67	2	0.55	2	0.475	2
21	0.83	2	0.84	2	0.67	2
28	1.1	3	1.09	2	0.9	3

TABLE 6.—*Results of Experiments on Thirty-Eight Rats*

	Nonimmersed Controls		Controls Immersed in Water		Transplants Immersed in Platinum	
Weeks	Average size, Mm.	Percentage Healed	Average Size, Mm.	Percentage Healed	Average Size, Mm.	Percentage Healed
1	44	0	21	33	25	55
2	67	15	38	44	25	55
3	92	15	54	11	46	22
4	120	15	80	11	76	11
5	150	15	105	11	101	11

placed for the same length of time in distilled water, and still others were transplanted directly into rats. The immersed tissues were kept at a temperature of 98.6 F. Thirty-eight rats were used. Nine received transplants from the colloidal platinum; 9 received those from the plain water, and 20 received direct implantations of the cancer tissue. The outcome is shown in table 6.

Since the difference in the percentage of tumors which healed after the implantation of fragments treated with platinum and those which healed after the implantation of fragments immersed in pure water is nil, and there is so little difference in the average growth week after week, there is probably no specific inhibitory effect following treatment with platinum. When one takes into account the small number of animals used, it is questionable whether the differences are significant. When compared with the unimmersed controls, each set of immersed

tissues is seen to have a slower rate of growth, but there is no reason to believe that this inhibitory effect is due to any cause other than the hypotonicity which must have resulted from the immersion of the cancer tissue in water for a period of two hours.

LYMPHOID REACTION TO COLLOIDAL PLATINUM

It was the purpose of experiment 13 to determine whether or not subcutaneous injections of colloidal platinum would cause an increase in the lymphoid response to subsequent implantation of cancer which might explain the beneficial effects of colloidal platinum observed in previous experiments. As the results obtained were negative, a detailed report will not be made.

It is interesting , however, that the subcutaneous injection of 0.5 cc. of colloidal platinum every other day for periods of over two months caused no apparent damage to the health of the rats. This indicates that it is nontoxic. As seen grossly and microscopically, most of the colloidal platinum seemed to be localized in the subcutaneous connective tissue, largely engulfed by tissue phagocytes.

There was some evidence that the injections of colloidal platinum caused a somewhat more rapid drop in the percentage of lymphocytes than is normal as the rats got older. That this is due to a lymphotoxic action is doubtful. Possibly a withdrawal of mononuclear phagocytes from the blood stream to the subcutaneous tissue where the particles of platinum are being engulfed is a factor.

HISTOLOGY OF SUBCUTANEOUS TISSUES INTO WHICH COLLOIDAL PLATINUM AND COLLOIDAL SILVER HAS BEEN INJECTED

To compare the reactions of subcutaneous tissue to injections of colloidal platinum and colloidal silver, respectively, 4 rats were given injections (experiment 14) of colloidal platinum (0.5 cc.) on the right side, and colloidal silver (0.5 cc.) on the left side. After periods of two, twenty-four, forty-eight and ninety-six hours, the skin and the subcutaneous tissue in the regions in which the injections were made were removed and sectioned.

At the end of two hours the silver in the subcutaneous tissue was seen to be surrounded by a profuse serous exudation, with leukocytes beginning to come in. Likewise, the platinum in the subcutaneous tissue was surrounded by a serous exudate and a beginning cellular invasion.

After twenty-four hours the silver was surrounded by a profuse leukocytic exudation. Some fibroblastic proliferation was also apparent. A yellow tinge to the silver suggested the formation of methemoglobin, possibly due to an injurious effect of ionic silver on the red blood corpuscles. The platinum was similarly surrounded by a profuse leukocytic exudation. Fibroblastic proliferation above the muscle layer was prominent.

At the end of forty-eight hours the silver was surrounded by leukocytes and a fibroblastic overgrowth. After the same length of time, the platinum was surrounded by a profuse fibroblastic overgrowth of a firmer appearance than that around the silver. Not much leukocytic exudation remained.

Finally, after ninety-six hours the particles of silver were surrounded by a rather serous fibroblastic proliferation (fig. 4, *4*). The large amount of serous exudation may have been a consequence of irritation caused by the slow formation

of ionic silver in the tissues. Another evidence of such a formation of ionic silver was the lysed cytoplasm of the muscle fibers near the silver. On the other hand, tissue adjacent to particles of platinum deposited for the same length of time gave no evidence of similar chemical injury.

It is evident that the foreign body reaction to colloidal silver and to colloidal platinum is much the same for the first twenty-four or forty-eight hours. Thus in both cases at two hours there is a beginning leukocytic infiltration around the metal, and at twenty-four hours there is a beginning fibroblastic proliferation which increases until at forty-eight hours it replaces the leukocytic exudation almost completely. The fibroblastic capsule, however, is thicker and denser in the case of the platinum. One difference noted between the tissues into which platinum had been injected and those into which silver had been injected is that in the latter from twenty-four hours on a yellow coloration is apparent around the mass of silver. This is due apparently to the formation of irritant ionic silver by the action of the tissue fluids. The pigment is probably a methemoglobin. Another evidence of the same fact is that in the tissues into which silver had been injected, especially at ninety-six hours, the striated muscle fibers near the silver underwent degenerative changes (fig. 4, *4*). The cytoplasm became basophilic and decreased in amount, so that in some places only the nuclei remained. These injurious effects on the normal tissues may possibly explain the apparently stimulative effects of colloidal silver on the growth of cancer, the silver producing an area of lowered tissue resistance so that the more resistant cancer cells grow freely. Since similar injurious effects do not occur around the injections of platinum, the foreign body reaction around the particles of platinum proceeds without the accompanying injury to the normal tissue. There is an additional difference between the effects of the two metals in that the connective tissue capsule formed around the platinum is more dense and more closely woven. This may be an important factor in the inhibitive action of colloidal platinum on the growth and spread of cancer tissue. In brief, unlike silver, the platinum apparently has no injurious chemical effect on the normal tissues, and in addition it calls forth an effective fibroblastic encapsulation.

ADSORBED OXYGEN OR HYDROGEN AND GROWTH OF CANCER

In view of the well known adsorptive capacity of colloidal platinum, it seemed advisable to determine whether or not its adsorptive capacity for oxygen might in some way be responsible for its cancer-inhibiting effects. The colloidal platinum was prepared (experiment 15) in the usual manner by sparking electrodes under distilled water. When ready the suspension was divided into two portions, one to have oxygen and the other hydrogen bubbled through it. The gases were bubbled through the colloidal platinum for three hours before the first injections, and two

hours before each of the succeeding injections. Seventeen rats were used: 9 for the oxygen-bubbled platinum suspension and 8 for the hydrogen-bubbled liquid. Injections were made intratumorally every other day. The results are presented in table 7.

TABLE 7.—*Comparison of the Effects of Adsorbed Oxygen With Those of Adsorbed Hydrogen on Growth of Tumors*

Suspension	Rat	Diameter of Tumor, Cm.			
		Start	First Week	Second Week	Third Week
Oxygen-bubbled colloidal platinum	1	1.1	1.5	1.8	2.0
	2	0.7	0.9	0.7	Rat dead
	3	1.0	1.0	1.1	1.3
	4	1.4	1.7	Rat dead	
	5	1.8	1.8	2.1	Rat dead
	6	1.0	1.0	1.3	Rat dead
	7	1.2	1.7	2.0	2.0
	8	0.7	0.8	0.9	0.4
	9	1.4	1.6	1.5	1.6
Average		1.14	1.33	1.43	1.2
Hydrogen-bubbled colloidal platinum	10	0.8	0.6	Healed	
	11	0.7	0.8	1.1	1.2
	12	1.4	1.4	1.4	Rat dead
	13	1.2	1.5	2.0	2.7
	14	1.4	1.4	1.5	Rat dead
	15	1.2	1.4	1.5	Rat dead
	16	0.9	0.9	1.0	Rat dead
	17	1.7	1.4	1.5	1.9
Average		1.16	1.18	1.43	1.7

Inspection of the table shows that the average sizes of the tumors of the two groups run about the same. It is evident that the oxygen-adsorbing property of colloidal platinum, at least so far as atmospheric oxygen is concerned, is probably not significant in its cancer-inhibiting properties. The only rat healed after three weeks (ten) was in the hydrogen group, but rat 8 in the oxygen group was well on the way to healing at the end of the experiment.

EFFECT OF SUBCUTANEOUS INJECTIONS OF COLLOIDAL PLATINUM ON SUBSEQUENT TUMOR TRANSPLANTS

In order to determine whether the action of colloidal platinum is directly on the tumor or on some more general mechanism of resistance of the body as a whole, 0.5 cc. of colloidal platinum was injected into the subcutaneous tissue of the posterior abdominal region of 8 rats every other day for eight days. After the fourth injection 2 implantations of cancer tissue were made in each of the rats into which platinum had been injected, one in the midst of the area of injection, and the other in the region of the thorax, where no colloidal platinum had been introduced. Eight control rats each received 1 implant. The results are presented in table 8.

It would appear from table 8 that while none of the rats used as controls was resistant to cancer, 3 of those that had previously received injections were resistant from the start. It is seen also that when one of the two cancers transplanted to an animal healed the other also healed. Waiving the possibility that 3 naturally immune rats had inadvertently been included among the treated animals, the results would seem to indicate a systemic rather than a local action on the part of the platinum, since the tumor not in contact with the platinum injected also healed. The fact that the anterior cancer regressed before the posterior cancer in the

TABLE 8.—*Effects of Previously Injected Colloidal Platinum on Tumor Transplants* *

After 14 Days			After 21 Days			After 35 Days		
Posterior Tumor	Anterior Tumor	Controls	Posterior Tumor	Anterior Tumor	Controls	Posterior Tumor	Anterior Tumor	Controls
Healed	Healed	0.5	Healed	Healed	1.0	Healed	Healed	1.7
Healed	Healed	0.4	Healed	Healed	1.0	Healed	Healed	0.3
Healed	Healed	0.6	Healed	Healed	0.7	Healed	Healed	0.8
0.7	0.6	0.4	1.2	1.0	0.5	0.4	Healed	2.3
0.5	0.6	0.7	0.5	0.4	0.7	1.4	2.0	...
0.7	0.6	0.5	0.8	1.0	1.0	0.9	1.4	...
0.5	0.6	0.8	0.7	1.0	0.7	1.7	1.8	...
0.7	0.5	0.5	1.0	1.3	Dead	1.7	1.7	Rat dead
Av. 0.62	0.58	0.55	0.84	0.94	0.8	1.22	1.725	1.285

* The size of the tumors is given in centimeters.

TABLE 9.—*Number of Cures and Size of Tumors in Rats Given Subcutaneous Injections of Colloidal Platinum Before Transplantation of Cancer and in Controls*

	After 7 Days		After 14 Days		After 21 Days	
	Average Size of Tumor, Cm.	Number Healed	Average Size of Tumor, Cm.	Number Healed	Average Size of Tumor, Cm.	Number Healed
Rats given injections	Anterior 0.57	0	Anterior 0.72	4	Anterior 1.20	4
	Posterior 0.47	1	Posterior 0.60	3	Posterior 1.03	4
Controls	Anterior 0.49	1	Anterior 0.66	8	Anterior 0.94	9
	Posterior 0.50	0	Posterior 0.62	7	Posterior 1.09	9

same rat had completely regressed (rat 5 in the thirty-fifth day tabulation) would make it seem unlikely that autovaccination resulting from the regression of the cancer in contact with the platinum was a factor in the regression of the anterior cancer. However, there were also evidences of local action, as at fourteen and twenty-one days the average size of the cancers in contact with the platinum was less than that of the anterior tumors not in contact.

Because of the small number of animals used, obviously the results of this experiment (16) are suggestive rather than conclusive. In view of this fact, it was decided to run an additional series. Forty rats, 20 given injections and 20 used as controls, were tested. The technic was the same as in the previous experiment with the exception that two implants instead of one were made in the controls. A summary of the results is presented in table 9.

It is evident from a study of table 9 that in this particular series of experiments the untreated rats fared better than the treated ones, since by the end of the third week 9 of them showed healing of both tumors as against 4 of the rats treated with platinum. The fact that in every case when one implant regressed the other did also at approximately the same time indicates that resistance to the growth of cancer is in some way a systemic phenomenon, even though not induced by the platinum. The somewhat slower growth of the posterior tumors implanted in the areas treated with platinum, however, indicates a local inhibitory effect of the platinum.

EFFECT OF LIMITED INTRATUMORAL INJECTIONS OF COLLOIDAL PLATINUM

To determine the effect of a limited number of early intratumoral injections of colloidal platinum on the later growth of the tumor, 20 rats were given two implants each, one on the abdomen and one on the thorax. After two weeks 9 rats with growing implants in which the anterior and posterior tumors were approximately the same size were selected for the test. Four injections of colloidal platinum (0.5 cc. each) were made into the posterior tumors over a period of a week and the injections were then discontinued. Distilled water was injected into the anterior control tumors. The tumors were measured weekly. The result in averages is shown in table 10.

TABLE 10.—*Persistent Curative Effect of Injected Colloidal Platinum*

	Week After Implantation; Average Diameter, Cm.				
	Third Week	Fourth Week	Fifth Week	Sixth Week	
Posterior (platinum-treated) tumor..	1.09	1.21	1.32	1.40	(2 healed)
Anterior (water-treated) tumor.....	0.94	1.13	1.73	1.94	(1 healed)
Difference in size.....	+0.15	+0.08	—0.41	—0.54	

The table shows that at the conclusion of the week during which the four injections were given, the tumors into which platinum had been injected averaged 0.15 cm. greater in diameter than the ones into which water had been injected. A week later the difference had shrunk to 0.08 cm., and by the end of the fifth week the tumors into which platinum had been injected averaged 0.41 cm. smaller than the ones into which water had been injected. The last measurements were made at the end of the sixth week, when the tumors into which platinum had been injected averaged 0.54 cm. smaller than the others, and two of the cancers had healed entirely as compared with one of those into which water had been injected. In one rat the tumor into which platinum had been injected regressed, while the one into which water had been injected continued to grow. This is the only case in more than 60 in which one tumor regressed without the other also regressing.

In this experiment (17) colloidal platinum not only again reveals an inhibitory effect on the growth of cancer but shows that this effect continues for a period of over three weeks after discontinuance of the injections. As the inhibition of the growth of the tumor continued after the inflammation had subsided, it was probably due largely to the fibrosis which had resulted from the early injections of platinum.

COMMENT AND CONCLUSIONS

The experiments that have been presented establish the fact that intratumoral injections of colloidal platinum lead not only to marked retardation of the growth of tumors, but often to regression and final disappearance. That some of the inhibitory effects may be due to mechanical injury is indicated by the fact that a slight degree of inhibition may follow injections of physiologic solution of sodium chloride, but the inhibitory effects of colloidal platinum are so much more pronounced that evidently, in addition to any general traumatic stimulus, some more specific reaction is involved. In contrast to the inhibitory effects of colloidal platinum, intratumoral injections of colloidal silver not only do not inhibit the growth of cancer, but favor it.

Histologic sections show that the colloidal platinum injected either intratumorally or subcutaneously is surrounded in less than an hour by an inflammatory exudation of leukocytes. This exudation is replaced largely within forty-eight hours by a proliferation of fibroblasts, which, in turn, lay down dense connective tissue. While colloidal silver apparently causes the same reaction at first, the sections show evidence of early injury to the surrounding normal tissue. This is indicated by yellow discoloration and lysis of the striated muscle cell cytoplasm. Such signs of injury are not seen in sections of tumors into which platinum has been injected.

That the effect of the platinum is not directly on the cancer cells is indicated by the fact that immersion of fragments of cancer in colloidal platinum before transplantation seems to cause little or no histologic or physiologic change beyond that attributable to the hypotonicity of the colloid, and subsequent implantation of such fragments is followed by but slightly retarded growth. Nor can the curative result be attributed to an increased lymphoid reaction, as the colloidal platinum injected causes no perceptible change in the usual lymphoid reaction which follows the implantation of cancer. The experiments also present no evidence that adsorbed oxygen or hydrogen is responsible for the cancer-inhibiting effects of colloidal platinum. As subcutaneous injections of colloidal platinum produce local sites of increased resistance to later implants of cancer, it is evident that in such cases one must attribute the inhibition of the growth of the tumor to local rather than to systemic factors.

The one interpretation consistent with all of the facts is that the inhibitory effects of colloidal platinum are due to the local inflammatory and fibrotic reactions which follow its injection, which, in turn, exert an inhibitory effect on the cancer, probably both by walling it off effectively from the surrounding tissues and by diminishing the supply of oxygen.

That inflammatory reactions inhibit cancer is a generally accepted conception, especially when the cancer is an implanted one, in which case it acts as a foreign body and incites the ordinary foreign body reaction, namely, leukocytic infiltration followed by fibrosis. Tyzzer [3] (1916), from his researches on resistance to implanted neoplasms, expressed the belief that a tumor is caused to regress by leukocytic infiltration around the fragment of tumor that has been rendered chemotactic by the action of cancer-immune bodies on it. The leukocytic infiltration, he maintained, is of the polymorphonuclear type if acute, and of the lymphocytic type if chronic. Likewise, da Fano [4] (1910) and Murphy [5] (1926) expressed the belief that leukocytic infiltration around implants of cancer is responsible for their regression. They stressed the lymphocyte in particular. Our sections of implants in susceptible and in resistant animals show that the leukocytic (mainly lymphocytic) infiltration around the cancer of a susceptible host is very sparse in comparison with that around the cancer of a resistant host.

Evidence from a different angle indicating that inflammation is inhibitory to the growth of cancer has recently been reported by Lohmann [6] (1931). From the work of Warburg [7] (1931) she came to the conclusion that the best means of therapy would be to decrease the oxygen, sugar and bicarbonate and to increase the carbon dioxide of the body. This was found impracticable because the normal tissues were also unfavorably affected. Since, however, it has been shown that the metabolism of the tissues during inflammation is least favorable for cancer cells—the oxygen, sugar and bicarbonate being low and the carbon dioxide high, and the area therefore acid—she undertook to determine exactly the effect of inflammatory exudate on the metabolism of cancer. This she did by means of Warburg's (1931) manometric methods. She found that in the inflammatory exudate glycolysis was practically destroyed, and that since oxidative processes were insufficient for survival the tissue died in from ten to fourteen hours. Her conclusion was that the ideal method by which to treat cancer would be to increase the inflammatory powers of the body. There is no known means at present to accomplish this systematically, but our experiments show that the local inflammatory reaction around the cancer can be increased by injections of colloidal platinum without destruction of the surrounding tissues.

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3. Tyzzer, E. E.: J. Cancer Research **1**:125, 1916.

4. da Fano, C.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **5**:1, 1910.

5. Murphy, J. B.: The Lymphocyte in Resistance to Tissue Grafting, Malignant Disease, and Tuberculous Infection, New York, Rockefeller Institute for Medical Research, 1926, monograph no. 21.

6. Lohmann, Ruth: Klin. Wchnschr. **10**:1799, 1931.

7. Warburg, Otto: The Metabolism of Tumors, New York, Ray Long and Richard R. Smith, Inc., 1931.

As colloidal platinum is capable of inciting an inflammatory reaction lasting about forty-eight hours, and in our experiments we injected it at such intervals, a continual state of inflammation must have existed in and around the cancer. It seems, therefore, that this is at least one of the factors in the inhibition of the growth of tumors.

As regards the rôle of fibrosis in resistance to cancer, it is impossible to cite all of the innumerable references throughout the literature in which the formation of connective tissue has been alleged to be of importance in checking the proliferation of cancer tissue. In this connection mention might be made of Woglum's [8] (1925) work on the histologic manifestations of resistance to implants of cancer. He described the regression of Jensen's rat sarcoma as occurring in three steps: (1) certain changes in the marginal cells and leukocytic infiltration, (2) definite necrobiosis and a fibrosis growing in from the investing capsule, and (3) fibrosis replacing the cancer. It is a well established pathologic observation that the greater the degree of fibrosis the less will be the rate of the growth of the cancer, a fact that accounts for the slow growth of a scirrhous carcinoma as compared with a medullary carcinoma. Since we have shown that injections of colloidal platinum cause fibrosis, this is obviously a second factor in the cancer-inhibitory effect of colloidal platinum.

Although colloidal silver causes inflammation and fibrosis, unlike platinum it also injures the surrounding normal tissue. Injured tissues, it is well known, are favorite sites for cancerous processes, so it seems highly probable that the inhibitory effects of the inflammation and fibrosis are offset in the case of colloidal silver by the injury to the surrounding normal tissue and the consequent impairment of its resistance to neoplastic invasion. That colloidal silver should be more injurious than colloidal platinum is to be expected when one considers the relative rapidity with which the silver ionizes in the tissues as compared with platinum. On the other hand, the experiments yield no evidence of injury to the cancer cells themselves by the ionic silver.

The observation that the immersion of fragments of cancer in colloidal platinum causes little or no histologic or physiologic changes in the tissue other than can be explained by its hypotonicity fits in with the inflammation-fibrosis conception, for while the fragments immersed in colloidal platinum grew slightly slower than those immersed in water, this was probably due to a slightly enhanced inflammatory and fibrotic reaction caused by a small amount of colloidal platinum adhering to the implanted fragments.

The lack of influence on the lymphoid system is apparently explained by our observation that colloidal platinum causes a leukocytic exudation

8. Woglum, W. H.: J. Cancer Research **9**:171, 1925.

which is not at all preponderantly lymphocytic. Moreover, the evidence points to the conclusion that colloidal platinum is local in its effects, probably because of its chemical inactivity. The experiments show likewise that the oxygen-adsorbing or hydrogen-adsorbing power of colloidal platinum is also probably inconsequential.

The inflammation-fibrosis interpretation is also borne out by the fact that subcutaneous injections of colloidal platinum produce an area of increased resistance to implants of cancer. It is evident that cancer would not grow so well in a bed of inflammation and fibrosis prepared by injections of colloidal platinum as in areas not receiving injections. The lack of a general systemic inhibitory effect is also to be expected when one considers the purely local action of the colloidal platinum.

The observation that the injection of physiologic solution of sodium chloride confers a slightly increased resistance also lends itself to explanation by the inflammation-fibrosis concept. It is evident that the mere injury by the needle and the tearing apart of the tissues by the injected fluid would cause a certain amount of inflammation which, of course, would be followed by an ingrowth of granulation tissue and some fibrosis. Obviously this inflammation is less in degree than that produced by the injections of colloidal platinum, since the latter apparently incites these reactions in a marked degree.

It may be said in conclusion, then, that colloidal platinum inhibits the growth of cancer by augmenting two of the body's defenses against cancer—inflammation and fibrosis. Furthermore, because of its relative chemical inactivity it does not injure any of the body's other defenses.

CONCENTRATION AND PRECIPITATION OF BILIRUBIN IN THE GALLBLADDER AND BILE DUCTS

EXPERIMENTAL STUDIES ON CATS AND DOGS

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Hospers [1] recently reviewed the literature on the experimental production of gallstones in various animals, and concludes that no method has yet been found that will consistently cause their formation, thus leaving the origin of biliary calculi still a matter of doubt. That inflammation per se can hardly be regarded as the primary etiologic factor in their occurrence is repeatedly observed at autopsy on the pyknic, and not infrequently on the athletic, human constitutional types, in whose normal-walled gallbladders one or more stones are often encountered in a highly concentrated bile. Numerous similar considerations lead one to surmise that there may well be an important physiologic factor in the formation of gallstones.

It is our purpose in this study to determine by an investigation of the normal physiology of the concentration of bilirubin in the gallbladder and bile ducts of the cat and the dog whether any mechanism exists which could provide a physiologic basis for the deposition of bilirubin on preexisting nuclei, rather than to seek the initial cause of the formation of calculi.

PHYSICAL AND CHEMICAL FACTORS IN THE PROBLEM

The physiologic importance of the gallbladder, so far as is known, has always been interpreted in terms of its power to concentrate bile. The visible manifestation of the degree of concentration attained is the intensity of the color, which is dependent on the relative pigment content of the bile. However, in addition to pigment, bile contains other colorless substances such as cholesterol, the bile acid derivatives, inorganic and organic salts of sodium, calcium and magnesium and, derived from the mucosa, mucin, all of which play a part in the process of concentration.

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1. Hospers, C. A.: Arch. Path. **14**:66, 1932.

The presence of these various substances makes the study of the concentration of bile difficult. Their physical properties are peculiar. Bile is an aqueous solution, yet its chief constituents per se are insoluble in water. That the free bile acids are not water-soluble has been pointed out by Horrall and Carlson.[2] The bile salts, however, derived from the action of alkali on the acids, are freely soluble in water. Horrall [3] stated that cholesterol also is insoluble in water, but is soluble in a bile salt solution, and Andrews and Dostal [4] stressed the integrity of a bile salt-cholesterol complex in the prevention of the precipitation of cholesterol in bile. That the cholesterol of bile exists chiefly in the colloidal state was noted by Ravdin and his co-workers.[5] Pure bilirubin, likewise, is insoluble in water, but since it is acidic in character,[6] it is sparingly soluble in alkalis and freely soluble in an alkaline solution having a p_H of 11 or more.[7] Van den Bergh [8] found that if an alkaline solution of bilirubin subsequently neutralized and used before the pigment precipitated out of solution (i. e., before the induction period had elapsed after the passing of the iso-electric point) was tested with Ehrlich's diazo reagent, no reaction occurred unless alcohol, alkali or the salt of some weak acid, such as a salt of cholic acid or its derivatives, was added, whereupon the usual color of the direct reaction would develop immediately.

Since Blankenhorn and Hoover [9] found two forms of bilirubin in icteric serum, one that would pass through an animal membrane and one that would not, thereby demonstrating that the one existed in the crystalloid state and the other in the colloid state, and Collinson and Fowweather [10] showed that the latter, or nondialyzable form, gave no reaction with the diazo reagent without the addition of alcohol, whereas the former, or dialyzable form, like the bilirubin of fresh bile, reacted at once in an aqueous medium, the use of the aqueous (direct) van den Bergh reaction to distinguish these two forms of

2. Horrall, O. H., and Carlson, A. J.: Am. J. Physiol. **85**:591, 1928.
3. Horrall, O. H.: Physiol. Rev. **11**:122, 1931.
4. Andrews, E., and Dostal, L. E.: Proc. Soc. Exper. Biol. & Med. **29**:1100, 1932.
5. Ravdin, I. S.; Morrison, M. E., and Smyth, C. M., Jr.: Ann. Surg. **89**:867, 1929.
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7. Harrop, G. A., Jr., and Barron, E. S. G.: J. Clin. Investigation **9**:577, 1931.
8. van den Bergh, A. A. Hijmans: Der Gallenfarbstoff im Blute, ed. 2, Leipzig, Johann Ambrosius Barth, 1928.
9. Blankenhorn, M. A., and Hoover, C. F.: Arch. Int. Med. **18**:289, 1916. Blankenhorn, M. A.: ibid. **27**:131, 1921.
10. Collinson, G. A., and Fowweather, F. S.: Brit. M. J. **1**:1081, 1926.

bilirubin appears to be legitimately established. Hence van den Bergh's experiment with the salt of cholic acid demonstrates that this bile salt can dissolve sufficient bilirubin to yield a visible immediate reaction in an aqueous medium.

It is to be inferred, then, that the primary requisite for the existence of the chief constituents of bile in a crystalloid state is a sufficient degree of alkalinity to convert bile acids to bile salts, thus providing a solvent for cholesterol and for small amounts of bilirubin. Hepatic bile is normally alkaline, but gallbladder bile is usually neutral; hence in the gallbladder the precipitation of a large portion of these solids must take place, creating a colloidal system.

For the assumption that the normal gallbladder concentrates cholesterol to any appreciable extent data are, as yet, lacking. Elman and Taussig [11] found about 221 mg. per hundred cubic centimeters in human gallbladder bile, and approximately 96 mg. per hundred cubic centimeters in human hepatic bile. Their cholesterol determinations on the gallbladder and hepatic bile of normal dogs averaged 69 mg. and 8.3 mg., respectively. Dostal and Andrews,[12] in their recent series of papers, reported no value for cholesterol above 83 mg. in dogs. The normal limits for human bile observed by McClure and Huntsinger [13] varied from 30 to 213 mg. In pathologic gallbladders, on the other hand, such as the "strawberry" gallbladder, Elman and Graham [14] found higher cholesterol levels.

Scant quantitative data are available on the variations in the concentration of the bile acid derivatives in the gallbladder, but that they may attain very high levels was shown by Ravdin and his co-workers,[5] who reported postmortem concentrations in gallbladder bile of the dog as high as 17,600 mg. Dostal and Andrews [12] found a variation in bile salt from 159 to 4,796 mg. in dogs.

METHOD OF STUDY OF THE CONCENTRATION OF BILIRUBIN

The present study concerns specifically the concentration of bilirubin as observed in the gallbladders and bile ducts of the cat and the dog. Two physical tests and three chemical tests have been applied; (*a*) the icteric index, which is a physical measurement of color intensity, (*b*) the refractive index, which is a function of density, (*c*) the aqueous (direct) van den Bergh reaction, which may be applied to distinguish water-soluble bilirubin (bilirubinate) from bilirubin in colloidal suspension, (*d*) the quantitative bilirubin (van den Bergh) and (*e*) the

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12. Dostal, L. E., and Andrews, E.: Arch. Surg. **26**:258, 1933.
13. McClure, C. W., and Huntsinger, H. E.: Boston M. & S. J. **194**:812, 1926.
14. Elman, R., and Graham, E. A.: Arch. Surg. **24**:14, 1932.

quantitative bilirubin (Salkowski) for comparison of results with those of the van den Bergh method. The Salkowski method, which is apparently an adaptation of the Gmelin reaction for quantitative colorimetry, in contrast with the method of van den Bergh, was found to yield eccentric results except with specimens of relatively low bilirubin content. It is analogous to the other methods that van den Bergh found unsatisfactory for such work.

Rous and McMaster,[15] using the Salkowski technic, were able to demonstrate in dogs concentrations in the gallbladder exceeding the concentration of the hepatic bile only fifteen times. Kalk and Schöndube,[16] on the other hand, using the van den Bergh method and obtaining their specimens by biliary drainage, were able to demonstrate a variation in the concentration of human bile of ninety times. The results of the latter two workers, however, are contestable because of the diluent action of duodenal and gastric secretions. Their maximum finding, nevertheless, was 1,000 mg. per hundred cubic centimeters, a figure more than five times as high as the maximum reported by Rous and McMaster for concentrated gallbladder bile of the dog.

We used twenty-three cats and nine dogs in our work and obtained thirty-three specimens of gallbladder bile and eighteen specimens of duct bile. Various maneuvers were executed to secure from the animals the most dilute and the most concentrated specimens normally obtainable. To eliminate the possibility that under ether anesthesia bile elaborated by the liver and obtained by ductal drainage after cholecystectomy might be more concentrated than normal as a result of a decrease in the water output of the liver, the dilute specimens were sought in the gallbladder itself as it was beginning to refill after its postprandial evacuation. A number of the animals were made to fast for from twenty-four to seventy-two hours to allow concentration to take place and were then given a meal of egg yolks. At varying intervals after this meal cholecystectomies were performed under ether anesthesia as quickly as possible and the contents of the gallbladders immediately examined. Frequently in this manner a very dilute specimen was secured, having a lower bilirubin content than any of the specimens from ductal drainage after cholecystectomy. Since there was no way of determining how rapidly the bile-laden gallbladders would empty in any given animal following the meal that broke the fast, it was a matter of chance to secure a specimen on refilling, but with this technic the very dilute specimens could confidently be considered to have entered the gallbladder

15. Rous, P., and McMaster, P. D.: J. Exper. Med. **34**:49, 1921.
16. Kalk, H., and Schöndube, W.: Med. Klin. **21**:1949, 1925.

from the liver after the concentrated bile had been evacuated. Maximum concentrations were sought in the gallbladders after sustained fasting for intervals of from twenty-four to one hundred and forty-four hours.

TECHNIC OF TESTS

Icteric Index.—Specimens of bile diluted with distilled water to a titer of 1 : 10 and occasionally of 1 : 20 were compared directly in the Duboscq colorimeter against the usual standard 1 : 10,000 solution of potassium dichromate, the standard being set at 30 mm. Occasionally it was necessary to employ a 1 : 100 solution of dichromate as the standard. Many refilling gallbladders contained very little bile, but amounts as small as 0.1 cc. could readily be drawn up into 1 cc. graduated pipets for dilution to volumes sufficient for use. Color qualities were always readily comparable. It is recognized that dilution impairs the accuracy of this test to some extent, but an effort was made to use as uniform dilutions as possible, the majority being 1 : 10. Van den Bergh has observed that the yellow color intensity of bilirubin solutions depends on their degree of alkalinity, the color for a given concentration intensifying as alkalinity increases.

Refractive Index.—The refractive index of undiluted bile was determined with the Abbé refractometer at 30 C. Changes in the density of solutions are determinable by changes in their refractive index.

Aqueous (Direct) van den Bergh Reaction.—To 1 cc. of fresh bile, diluted or undiluted, in a graduated centrifuge tube, 0.5 cc. of Ehrlich's diazo reagent[6] was added. Frequently a slight to heavy coagulum forms, but does not impair the perception of the change in color, especially if the reagent is overlayed on the bile. The more dilute the bile, the less is the coagulum. Even in very high dilutions the change in color could easily be detected. When the reaction is negative, it can be made positive by the addition of a drop of dilute strong alkali, but specimens to which alkali has been added are useless for subsequent quantitative determinations because of the development of a green color on the addition of alcohol.

Quantitative Bilirubin (van den Bergh).—After the determination of the aqueous (direct) van den Bergh reaction, the centrifuge tube was filled to the 5 cc. mark with 95 per cent alcohol. Since proteins are not normally present in bile, it is not necessary, as with serum, to add saturated ammonium sulphate. On the addition of the alcohol the coagulum resulting from the addition of the diazo reagent immediately disappears, and the solution clears. After a thirty minute interval to allow full development of color, readings were made in the Duboscq colorimeter against van den Bergh's cobalt sulphate standard, and the bilirubin content was computed from the several dilutions. It was found in trial dilutions of higher than 1 : 20 titer that frequently the maximum color intensity developed far more quickly than in the lower dilutions, and that undiluted bile, even after long intervals, often failed to attain the proper color intensity, especially when the bile was concentrated. It is well known that serum proteins adsorb direct positive bilirubin, and van den Bergh has shown that it is necessary to dilute serum in order to break up this adsorption compound before determining its bilirubin content, if a high degree of accuracy is desired. Since it now appears that bile also must be diluted to facilitate the accurate determination of its bilirubin content, it is probable that by this dilution adsorption compounds of bilirubin with the colloidal bile acids are broken up.

Quantitative Bilirubin (Salkowski).—This method was used according to the technic described by Rous and McMaster. The results were eccentric and not sufficiently consistent with the results of the other tests to be valid. Color incomparability was extreme, with qualities that could not be matched with the standard.

CORRELATION OF FINDINGS AND COMMENT

Correlation of Icteric Index with Quantitative Bilirubin.—The general correlation of the icteric index with the quantitative bilirubin (van den Bergh) shows a progressively increasing variation in the amount of bilirubin which may be present for any given icteric index as concentration increases. This is not remarkable in consideration of the fact that a physical test is here correlated with a chemical one, each being based on an entirely different principle. This variation may be expressed in terms of the bilirubin-icteric index ratio, which in both the cat and the dog averages lower for gallbladder bile than for bile obtained from the hepatic ducts after cholecystectomy, as shown in table 1.

TABLE 1.—*Variation in the Bilirubin-Icteric Index Ratio*

Bilirubin-Icteric Index Ratio	Cats	Dogs
Range of ratio in duct bile	0.097-0.182	0.115-0.184
Range of ratio in gallbladder bile	0.062-2.0	0.067-0.167
Average ratio for duct bile	0.137	0.157
Average ratio for gallbladder bile	0.097	0.121

No adequate explanation of this phenomenon can be suggested. In a number of animals the specimens from the gallbladder were early refillings from the liver and were obtained presumably before appreciable absorption of water by the gallbladder had taken place, and frequently hepatic bile in fasting animals was found to be almost as highly concentrated as that in the gallbladder; hence the division may be regarded as somewhat arbitrary in many cases.

Correlation of Icteric Index and of Quantitative Bilirubin (van den Bergh) with Refractive Index.—An analysis of the changes in the refractive index as the icteric index and quantitative bilirubin rise reveals a striking phenomenon. The minimum refractive index was found when the quantitative bilirubin was 40 mg. per hundred cubic centimeters and the icteric index 400. Below these points the first maximum refractive index was obtained on the most dilute specimen of bile, and from this initial point the refractive index declined sharply to the minimum. As the level of bilirubin of 40 mg. and the icteric index of 400 were exceeded, the refractive index rose sharply to attain at once its second and final maximum, remaining constant thereafter in spite of further concentration of bilirubin and increasing intensity of color. A graph of this curve, with the values for its icteric index or the quan-

titative bilirubin as the abscissae and the values for the refractive index as the ordinates, closely resembles the algebraic sign used to designate the square root of a number. Two or three points alone do not appear to conform to such a curve and are recognized exceptions.

The range of refractive index for all specimens of bile examined lies between 1.33504 and 1.37030, and the refractive index of the most dilute bile was 1.35295. Distilled water at 25 C. gives a refractive index of 1.33251. It is apparent that at the critical concentration of bilirubin in bile (40 mg. or an icteric index of 400) the density of bile is but slightly above that of distilled water, and, therefore, since it is known to contain solids, these solids must exist at this point chiefly as suspended colloids incapable of affecting density, the bile acid derivatives as bile acids rather than as their sodium salts, and cholesterol and bilirubin likewise in a state of suspension. At this point the aqueous (direct) van den Bergh reaction was observed to be negative, a fact consistent with the assumption that bilirubin, at least, has reverted to the colloidal state. In three other specimens falling near this point the van den Bergh reaction was also negative.

These findings imply that there exist in the process of bile concentration (*a*) a critical concentration at which bilirubin precipitates out of solution, possibly in association with the precipitation of bile acids and cholesterol, and (*b*) a limit of crystalloid concentration attained immediately when this critical concentration is exceeded, affecting all the solids characteristic of bile, beyond which the excess of these solids can be present only as suspended colloids or undissolved crystals. Were the process of concentration a simple matter of progressive increase in soluble substances, the refractive index, which for a given liquid increases with increasing density as more and more solute goes into solution, would continue to rise progressively as with sugar solutions. This phenomenon in bile bears all the characteristics of the pectization and peptization of colloids,[17] or, in other words, the precipitation of a disperse phase at a critical concentration followed by partial redispersion as concentration continues.

Early bile, containing the least pigment per unit volume, has a relatively high refractive index; hence the proportion of its solids existing in a state of true solution must be relatively great, and since hepatic bile is alkaline, and therefore contains bile salts, these salts act as a solvent for cholesterol and for a small amount of bilirubin. Thus the latter two substances, tending to be colloidal under ordinary physiologic conditions because of their insolubility in water, could be converted to the crystalloid state, thereby becoming excretable through the paren-

17. Crocker, J. C., and Matthews, F.: Theoretical and Experimental Physical Chemistry, New York, The Macmillan Company, 1928.

chyma of the liver by the solvent action of the bile salts which originate there. It is well known that no excretory organ normally excretes colloids as such from the blood stream, for the physiology of excretion as well as of assimilation implies a mechanism of solubility.

Concentration of Bilirubin During Fasting.—The gallbladder bile was examined in three cats after one day of fasting, in two cats after two days, in two dogs and four cats after three days, in two dogs after five days and in three cats after six days; none of the animals received a preliminary meal. The maximum icteric index (4,000) was found in the gallbladder of a cat after a fast of only one day, and the maximum bilirubin content (533 mg.) was found in the gallbladder of a cat which had

TABLE 2.—*Summary of Data on Concentration*

	Icteric Index	Bilirubin van den Bergh, Mg. per 100 Cc.	Bilirubin Salkowski, Mg. per 100 Cc.	Refractive Index
Dogs				
Maximum	2,000	326.0	45.7	1.37030
Minimum	75	6.4	10.8	1.33504
Concentration factor	26.7	50.9	4.24	
Cats				
Maximum	4,000	533.0	166.8	1.36780
Minimum	100	13.2	8.6	1.33980
Concentration factor	40	40.4	19.4	
Both animals				
Maximum	4,000	533.0	166.8	1.37030
Minimum	75	6.4	8.6	1.33504
Concentration factor	53.3	83.3	19.4	

fasted for three days. With the exception of the latter animal, no progressive concentration of bilirubin could be demonstrated quantitatively or by color intensity after the first twenty-four hours of fasting. The failure of further concentration to occur after twenty-four hours may readily be explained by the constant observation at operation that in all animals fasting longer than this the gallbladder and bile ducts were noticeably dilated, and bile had already leaked into the duodenum. Puestow [18] observed that rarely did leakage occur from the duodenal ampulla during fasting in dogs when, after gastrojejunostomy, an isolated segment of duodenum, including the ampulla, was surgically incorporated in the abdominal wall to allow direct visualization. In our animals there was no disturbance of normal anatomic structure prior to operation.

The fact that bile which drained from the hepatic ducts after longer intervals of fasting was highly concentrated would imply that concentration can occur in the ducts as well as in the gallbladder, especially after the concentration in the gallbladder has attained its maximum in these animals. A compensatory decrease in the output of water from the liver must also be considered as a possibility.

18. Puestow, C. B.: Arch. Surg. **23**:1013, 1931.

Refractive Index During Fasting.—After the first twenty-four hours of fasting no further increase in the density of bile in the gallbladder could be detected by changes in the refractive index, for even after six days of fasting the refractive index did not exceed the value it had attained in twenty-four hours.

Variations in the Character of the van den Bergh Reaction on Fresh Bile.—Although the recognized immediate reactions predominated when the diazo reagent was added to fresh bile, variations were not uncommon, and it may be stated that this reaction on fresh bile may simulate any of the several types of reactions described for icteric serums, such as immediate blue-violet and red reactions, slow and delayed reactions and the negative reaction. Van den Berg described a delayed reaction on fresh bile after heating.

SUMMARY

In a study of the concentration of bilirubin in the gallbladders and bile ducts of twenty-three cats and nine dogs the most dilute specimens were obtained, not from the hepatic ducts after cholecystectomy, but from the gallbladders as they were refilling after postprandial evacuation, and the most concentrated specimens were secured from gallbladders after the animals had fasted for from twenty-four to one hundred and forty-four hours. Hepatic duct bile after cholecystectomy invariably yielded a higher bilirubin content and icteric index than the early refillings from the gallbladders.

The factor of bilirubin concentration for dogs was found to be 50.9, for cats, 40.4 and for both animals together, 83.3. According to the work of Kalk and Schöndube, the factor for either of these animals is appreciably less than that found for man.

The bilirubin-icteric index ratio averages lower for gallbladder bile than for bile obtained from the hepatic ducts after cholecystectomy in these animals.

Correlation of the refractive index with the quantitative bilirubin or the color intensity of bile indicates that a critical concentration exists at which bilirubin tends to precipitate out of solution. When this critical concentration is exceeded, the density of bile at once attains its maximum, being constant thereafter in spite of continued concentration. These findings indicate that a limit of crystalloid concentration exists, affecting bilirubin, bile acid derivatives and cholesterol, and effective when the critical concentration is exceeded, and that their further concentration can be only as suspended colloids or undissolved crystals.

Studies on the concentration of bile during fasting showed that the maximum level of bilirubin is usually attained in the gallbladder within twenty-four hours, and that after this interval hepatic bile leaks into

the duodenum. The density was found not to increase, even after six days of fasting, above the value attained in twenty-four hours.

The aqueous (direct) van den Bergh reaction on fresh bile simulated any of the various types of reactions described for icteric serums, including immediate blue-violet and red reactions, slow and delayed reactions and the negative reaction.

Since gallstones are seldom found in the cat and the dog, the physiologic precipitation of bilirubin during its concentration in the normal gallbladders of these animals cannot be regarded as the exciting cause in the origin of biliary calculi, but affords a physiologic basis for deposition of the pigment on preexisting nuclei.

WATER IN THE LUNGS OF DROWNED ANIMALS

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In the ordinary process of resuscitation the presence of water in the lungs is entirely disregarded. From a practical standpoint this may be excusable, but unfortunately it leads to a great misunderstanding and underestimation of the part played by water in drowning.

There are three major problems that need clarification: (1) the amount of water taken into the lungs during drowning, (2) the distribution of the water in the lungs and its disposition, and (3) the blocking effect of water in the lungs when an attempt is made at reestablishment of respiration.

The first two of these problems have been studied directly or indirectly by many investigators.[1] The last problem, however, has evidently never been experimentally approached. It is hoped that this experimental study in the field of the third problem will materially clarify the whole phenomenon of drowning.

Rats, guinea-pigs and cats were used. The experiments were carried out in an aquarium with flat walls enabling one to observe easily and accurately all stages in drowning. Although the behavior of the animals varied somewhat on being submerged, the whole phenomenon could be divided into five stages:

1. An immediate struggle for freedom; sometimes a surprise inhalation
2. Suspension of movement; exhalation of a little air and frequent swallowing
3. A violent struggle for freedom
4. Convulsions; expiration of air and spasmodic inspiratory efforts with the mouth wide open; disappearance of the reflexes
5. Death

The most important phase is the fourth, during which the air is expelled and violent inspiratory movements are made. It is on the observation of this phase in particular that some of the conclusions in this paper were deduced. At this point the observation was close, par-

1. (*a*) Curry, J.: Observation on an Apparent Death from Drowning, London, E. Cox & Son, 1815. (*b*) Bergeron, G., and Montano, J.: Ann. d'hyg. **48**:332, 1877. (*c*) Winternitz, M. C.: Collected Studies on the Pathology of War Gas Poisoning, New Haven, Conn., Yale University Press, 1920, p. 145.

ticular attention being given to the accurate counting of the inspiratory attempts before the fifth phase, death, set in.

AMOUNT OF WATER TAKEN INTO THE LUNGS DURING DROWNING

The computation of the amount of water taken into the lungs of a drowned animal is based on the following procedure:

1. Weigh dry animal.
2. Wet for two minutes.
3. Let water drip from animal for 90 seconds.
4. Weigh wet animal.
5. Etherize, ligate esophagus, revive.
6. Submerge for three minutes.
7. Let water drip from animal for 90 seconds.
8. Weigh the animal.
9. Weigh the lungs.
10. (Used in place of 6) Strangle the animal or destroy its medulla.

TABLE 1.—*Estimations of Water Taken into Lungs of Animals in Drowning*

Condition of Animal	Animal	Weight of Animal, Gm.				Weight of Lungs
		Dry	Wet	After Drowning	Difference	
Esophagus not tied	1	101	102	105.5	3.5	1.9
	2	114	116	122	6.0	1.7
Esophagus ligated	3	121	122.5	.....	...	1.5
	4	127	131.6	135.1	3.5	1.85
	5	120	123.5	125.5	2.0	1.0
	6	119	122.5	124.1	1.6	1.0
	7	125	129.3	132.7	3.4	1.05
	8	103	110.8	114.6	3.8	1.3
	9	119	122.7	124.4	1.7	0.8
	10	160	167	169	2.0	1.1
	11	160	164	169.1	5.1	1.3
	12	95	99.5	101.4	1.9	0.5
Death due to strangulation after etherization	13	104	107.3	107.9	0.6*	0.4
Death due to destruction of medulla	14	106	.....	.....	...	0.4

* The control experiments showed a possibility of a maximum error of 0.7 Gm. for an average rat. Case 13 illustrates this, since there was an increase in weight of 0.6 Gm. although the rat was dead before drowning. Therefore the average amount of water taken in should be between 19.1 and 22.6 cc. per kilogram of body weight.

Table 1 shows the results of twelve typical drownings, one destruction of the medulla and one strangulation.

The difference between weights before and after drowning in the cases in which the esophagus was ligated represents the amount of water that has entered into the body through the respiratory passages. Table 1 shows that the weight of the lungs is much less than the weight of the water taken in, and therefore one concludes that the bulk of the water inspired was absorbed into the blood stream. This was noticed by Falk in 1869 and was used as the basis for a proof of drowning by Revenstorf.[2] The amount of water thus entering the respiratory

2. Revenstorf: München. med. Wchnschr. **45**:1880, 1902.

passages varies from 12.5 to 36.9 cc. per kilogram of body weight, or an average of 22.6 cc.

In experiments performed by Winternitz and Smith,[1c] 20 cc. of physiologic solution of sodium chloride per kilogram of body weight was introduced by gravity into the lungs of an anesthetized dog. The animal recovered and appeared perfectly normal. The fact that smaller quantities of water per kilogram of body weight were fatal to the rats in my experiment can be easily explained. In the first place, the dog suffered only from partial asphyxiation; second, the time taken for the introduction of the water into the respiratory passages of the dog was longer; third, the dog was able to develop a relatively greater inspiratory force than the rats. It is thus found that when the water is introduced slowly over a long period of time, giving the blood stream sufficient time to absorb it, the amount of water introduced may far exceed that which would ordinarily drown the animal given a shorter period of time, as is the case in drowning.

DISTRIBUTION OF WATER IN THE LUNGS

On examination of the lungs and respiratory passages of the drowned animals, the trachea and bronchi were always found filled with water and froth. The alveoli, however, contained little or no water. The explanation of this is that the enormous surface area and great absorbing power of the pulmonary endothelium freed the microscopic alveoli from water, passing it into the blood stream.

To investigate the distribution of water in the lungs further, drownings were caused in a colored solution (ordinary Waterman's ink or india ink being used). In every case, colored water and froth were found in the trachea and bronchi, and colored areas were easily seen on the surface of the lungs. The colored areas were especially frequent on the lower lobes, sometimes occupying half of the mediastinal and diaphragmatic surfaces; occasionally the apexes were also colored.

Similar experiments have been made by other investigators—as early as 1778 by Gardane [3] and 1815 by Curry [1a]—the results being somewhat conflicting. It is believed that atypical cases in the present research may explain the contradictory results of these previous experimenters. One of these atypical cases is described at this point. A female rat weighing 237 Gm. was submerged in colored liquid for seventy-five seconds. When removed the body felt rigid, and the heart was still beating. After one minute and fifteen seconds of artificial respiration, breathing began, and forty-five seconds later the rat made an attempt to walk. Then the animal was rapidly killed and an autopsy made. The esophagus and stomach contained some colored water. No colored liquid was found in the lungs, which were a brick red. As it was impossible to

3. Gardane, cited by Cumston, C. G.: M. Rec. **95**:235, 1919.

witness the behavior of the rat when it was immersed in the colored water, I can only surmise what happened. I believe that the rat suspended respiration for the entire seventy-five seconds. There is no doubt but that if the time had been lengthened, drowning would have followed, and colored liquid would have been found in the lungs. Additional experiments of this type proved that there were rats which would hold their breath for a considerably longer time than the average, and which would immediately start breathing on being taken from the water, sometimes without the assistance of artificial respiration. These same rats, when they were later submitted to the same drowning experiment, with a lengthened period of immersion, invariably followed the typical examples cited in table 1.

BLOCKING EFFECT OF WATER

An attempt was made to inflate the lungs of animals drowned in colored liquid. These lungs could not be inflated in the same manner as lungs excised from animals killed by other means. The stained areas always remained depressed, while the uncolored portions inflated in a natural manner. This procedure proved that air, even under the great pressure of an attempted inflation, could not reach these parts owing to the resistance of air bubbles in water (froth) and mucus which blocked the minute passages. It is well known that the resistance offered by air bubbles may be very great; attention is called to air embolisms in the circulatory system which often stop the circulation.

Mention was made of mucus. This was found present in some instances but not to an appreciable amount, and therefore it is not considered separately from water in these results.

To procure objective data concerning the blocking of the respiratory passages, it was decided to measure the pulmonary pressures developed during artificial respiration in rats and guinea-pigs killed by drowning and in those killed by other means. The following procedure was used: A water manometer was connected to the trachea of the dead animal. The chest was then squeezed to the maximum and released, positive and negative readings being taken. The results are shown in table 2.

In table 2, it may be seen that in cases of drowning the inspiratory and expiratory pressures are appreciably lower than when death occurs through other causes. This decreased pulmonary pressure during artificial respiration depends also on decreased pulmonary capacity due to the elimination of some parts of the lung through blocking, and also to decreased elasticity of the lung caused by edema. The blocking effect of water may also be estimated by the forces required to blow equal amounts of air into the lungs of drowned animals and those killed by other means. It required 50 per cent more pressure when drowned animals were used. I conclude from this that the blocking effect of water has been the cause of many failures of resuscitation. In the

present study, resuscitation was practiced on forty-one animals. Sixteen attempts were failures; thirteen animals were completely revived; the remainder, twelve, started to gasp, making frantic but unsuccessful efforts to get air into their lungs, the result being death in from two to four minutes on cessation of the heart beat. Water never escaped from the lungs of a drowned animal that was held by the tail, head down, but after a prolonged and vigorous period of artificial respiration water sometimes exuded from the trachea. Auscultation of the revived rats demonstrated the presence of water in the lungs. This was also

TABLE 2.—*Pulmonary Pressures Developed During Artificial Respiration in Animals Killed in Various Ways*

Animal Used	Weight, Gm.	Cause of Death	Pressure, Mm.	
			Expiratory	Inspiratory
Rat 1	205	Blow on head	+20	—16
Rat 2	210	Strangulation	+17	—14
Rat 3	359	Drowning	+ 4	— 4
Rat 4	258	Drowning	+ 5	— 6
Rat 5	260	Drowning	+ 4	— 5
Guinea-pig 6	370	Strangulation	+34	—20
Guinea-pig 7	350	Strangulation	+24	—36
Guinea-pig 8	360	Drowning	+18	—12
Guinea-pig 9	380	Drowning	+16	—10
Guinea-pig 10	379	Drowning	+16	—11

TABLE 3.—*Relation of Number of Inhalations Under Water and Size of Rat to Prognosis*

Number of Inhalations Under Water	Rats Weighing Under 100 Gm.		Rats Weighing About 200 Gm. and Over	
	Died	Revived	Died	Revived
1	0	3	0	3
2	8	2	0	2
3	8	0	2	4
4	..	..	1	0
7	..	..	1	0

supported by autopsies of rats revived after drowning in colored water, but obviously the revived animals inhaled relatively less water than those that could not be revived. The relation between the number of inhalations under water, the size of the animal and the prognosis was established during the experiments, and the results are given in table 3.

From this one may conclude that a larger rat can make more inhalations with safety than a smaller rat, there being no possibility of reviving a rat weighing under 100 Gm. after three inhalations, whereas rats weighing about 200 Gm. had a fair chance for revival. The paramount reason for this difference is found in the greater chest development, making possible greater inspiratory effort.

SUMMARY

Water enters the lungs on drowning, the amount varying from 12.5 to 36.9 cc. per kilogram of body weight. Drowning in colored water showed that water may reach any part of the lungs. Blocking of the respiratory passages by water and froth decreases the effectiveness of artificial respiration from two to four times. The number of inhalations made under water varies from one to nine, depending on the body size, larger animals being able to make more inhalations under water with safety than smaller animals.

BLOOD DIASTASE IN CANCER

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Somogyi's [1] improved methods for the determination of blood diastase permit the estimation of very low values and relatively slight variations, with a greater degree of accuracy than has been possible with other methods. My associates and I have applied this method to the study of the blood content of diastase in malignant disease, with the purpose of determining whether or not there is any deviation from the normal, and if there is, whether or not this difference could serve as a diagnostic or a prognostic test.

A review of the literature revealed a dearth of studies of the relationship of the blood diastase to malignant disease. In 1919, DeNiord and Schreiner [2] made an analysis of the blood diastase content in fifty-two cases of malignant disease. They concluded that the blood diastase content in malignant disease was in no way characteristic, and observed no constant change in the blood diastase twenty-four hours following roentgen exposure. The method for the determination of diastase used by these authors was that of Myers and Killian,[3] which, in our experience, does not yield quantitative information as to diastatic activity.

METHOD

The method employed in the present investigation is, briefly, as follows: To 5 cc. of 1.5 per cent starch paste, prepared by the boiling of raw rice starch, are added 2 cc. of 1 per cent solution of sodium chloride and 1 cc. of fresh blood serum (or plasma), and the mixture is incubated for thirty minutes at 40 C. Diastatic action is immediately terminated at the end of the period of incubation by the addition of 1 cc. of 5 per cent copper sulphate. The proteins are precipitated by Somogyi's copper method,[4] which is known to yield true sugar values. In the filtrate the sugar is determined by the Shaffer-Hartmann method, as modified by Shaffer and Somogyi.[5] The value obtained represents the sum of the sugar formed from starch by diastase plus the native sugar content of the serum. The latter is determined in a separate sample and deducted. The difference represents the reducing sugar formed by diastase. The diastatic activity is expressed as the

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From the Research Department of the Barnard Free Skin and Cancer Hospital and the Laboratory of the Jewish Hospital.

1. Somogyi, Michael: Proc. Soc. Exper. Biol. & Med. **29**:1126, 1932.
2. DeNiord, H. H., and Schreiner, B. F.: Arch. Int. Med. **23**:485, 1919.
3. Myers, V. C., and Killian, J. A.: J. Biol. Chem. **29**:179, 1917.
4. Somogyi, Michael: J. Biol. Chem. **90**:725, 1931.
5. Shaffer, P. A., and Somogyi, Michael: J. Biol. Chem. **100**:695, 1933.

amount of reducing sugar, in terms of milligrams of dextrose, produced by 100 cc. of blood serum in thirty minutes' incubation at 40 C. under the conditions just described. Thus, for example, a diastatic activity of 75 means that 100 cc. of the respective serum, under our standardized conditions, yields sugars which reduce as much copper as does 75 mg. of dextrose.

RESULTS

In healthy persons a wide variation in the diastatic activity is observed, ranging from 75 to 200, the average being about 125. However, great as these variations are, the diastatic activity of a given person, during health, shows a remarkable constancy over long periods, some of the observations extending over a year. Fluctuations and a decrease in the blood diastase of a given person, as was observed in Somogyi's laboratory,[1] occur only in pathologic conditions, particularly in pulmonary and hepatic infections and in some pyogenic processes. The deviations from the normal in these cases are in the direction of a conspicuous decrease of the blood diastase to a value below the lowest normal levels. In the study of a large series of clinical cases, some cases of cancer were observed to fall into this class. In view of these findings, particularly since there is practically no satisfactory report of such studies, it was deemed of interest to extend the investigations to a large number of patients with cancer, in different stages of the disease, attempting to correlate, if possible, the clinical course and the fate of the patient with changes in the level of the blood diastase.

In this investigation, eighty-one cases of malignant disease were studied. In all but five instances there was a microscopic diagnosis of the tumor. It was planned to determine the blood diastase as soon as the patient came under observation and at frequent intervals after treatment was instituted. It was not always possible to make the first determination before treatment had begun; in other cases it was impossible to make more than one estimation. The study included cancers of various organs; most of them, however, occurred about the mouth and the female generative organs. The neoplasms were chiefly of the squamous cell carcinoma type. In addition, there were several adenocarcinomas, particularly of the breast and the abdominal viscera. In table 1 is listed the number of cases of each type of cancer, together with the number of cases of normal, low and high blood diastase found with each type of tumor. Since these figures refer to the first determinations of diastase made, a tabulation of the number of changes from normal to low, or vice versa, is presented at the same time. Eight patients with normal blood content of diastase when first examined eventually showed the diastase of the blood to be abnormally low, while in five cases with low values at first, subsequent normal values were found. The table demonstrates that the proportionate distribution of normal and low values is fairly uniform for each type of cancer

observed. Thus, one cannot infer that location or type of cancer influences the level of the blood diastase. It may also be stated that in these cases the grade of malignancy of each tumor showed no correlation with the diastase content of the blood.

High Blood Diastase.—Several interesting facts about the level of the blood diastase in cases of cancer, as demonstrated by table 1, should be pointed out. All told, eighty-one cases of malignant disease were studied. Of these, five cases showed high diastase. Two of these five cases were proved to be instances of obstruction of the pancreatic duct, the progressive rise in the level of the blood diastase being spectacular. High blood diastase under these circumstances has been described by

TABLE 1.—*Analysis of Cases*

Location and Type of Tumor	Number of Cases	Diastase			Subsequent Decrease from Normal	Subsequent Increase from Low
		Normal	Low	High		
Squamous cell carcinoma of cervix	12	8	4	0	..	..
Adenocarcinoma and sarcoma of uterus	3	2	1	0	..	..
Squamous cell carcinoma of vulva	2	0	1	1	..	..
Adenocarcinoma of ovary	1	0	1	0	0	1
Squamous cell carcinoma of lip	7	6	1	0	0	1
Squamous cell carcinoma of jaw, mouth, tonsil and nasopharynx	12	8	3	1	0	2
Adenocarcinoma of breast	10	7	2	1	2	0
Adenocarcinoma of ileum, sigmoid, rectum and anus	6	6	0	0	2	0
Adenocarcinoma of lung	3	1	2	0	1	0
Adenocarcinoma of stomach, liver and pancreas	14	7	5	2	2	1
Adenocarcinoma of parotid	2	1	1	0	1	0
Squamous cell carcinoma of nose, larynx, neck and hand	4	4	0	0	..	..
Carcinoma of esophagus	1	1	0	0	0	0
Lymphosarcoma	1	1	0	0	0	0
Basal cell carcinoma of temple	2	1	1	0	0	0
Unclassified	1	1	0	..	..	..
Total	81	54	22	5	8	5

Elman [6] and others. Two other cases of this group of five were first examined shortly after radiation therapy, and, as will be discussed later, there is a definite relationship between radiations and the increase in blood diastase. In one case there was no apparent explanation for a high blood diastase. In this case, however, two days before death the blood diastase had fallen to a normal level. A summary of each case is of interest.

CASE 1.—A man, aged 76, had a squamous cell carcinoma of the cheek, mouth, lip and mandible of two months' known duration. High voltage roentgen therapy was given on May 10, 13 and 20, 1932. On June 3, the blood diastase was 297. He died on July 28. (There was a high blood diastase within two weeks after high voltage roentgen therapy.)

6. Elman, R.: Arch. Int. Med. **48**:828, 1931.

CASE 2.—A woman, aged 70, had a carcinoma of the vagina, with cerebral metastases. Exposure to 1,050 mg. hrs. of radium was made on July 19, 1932. On August 5, the blood diastase was 319. She died on August 14. (There was a high diastase within three weeks after radium therapy.)

CASE 3.—A woman, aged 66, had a carcinoma of the pancreas with peritoneal metastases. On Jan. 21, 1933, the blood diastase was 286; on January 26, 438, and on January 31, 779. The patient was progressively losing ground. (There was an obstruction of the pancreatic duct.)

CASE 4.—A man, aged 71, had an abdominal mass due to carcinoma of the gallbladder. One day prior to exploratory laparotomy the blood diastase was 460. Obstruction of the pancreatic duct was confirmed by operation.

CASE 5.—A woman, aged 65, had a recurrent adenocarcinoma of the breast, graded 4. Partial resection had been performed one year previously. On July 30, 1932, the blood diastase was 264. On August 6, radical resection of the breast was performed. On August 8, the blood diastase was 86. The patient died on August 10. This case is the one for which we can find no tentative explanation of the high diastase.

Low Blood Diastase.—Of great interest is the observation that in twenty-two of the eighty-one cases (27.4 per cent), the blood diastase was definitely low. This becomes more striking when it is observed that in eight additional cases in which the values were normal at the initial examination the blood diastase was found subsequently to be below normal. Indeed, one of the most significant observations is the tendency for the level of the blood diastase in any given case to fluctuate markedly at various stages of the disease or treatment, contrary to Somogyi's observations of the level of the blood diastase in healthy persons.

It becomes pertinent at this time to inquire into the cause of decreased blood diastase in the cases in which it was observed. In health, low diastase is not seen. It has already been mentioned that marked decreases have been observed by Somogyi in septic processes, particularly in pulmonary and hepatic infections. When these conditions complicate malignancy, the blood diastase may be low, and when, as in the case to be described, the infection subsides, the diastase level may rise to normal.

CASE 6.—A woman, aged 67, had had symptoms of indigestion since April, 1932. Exploratory laparotomy, performed on May 2, established the diagnosis of carcinoma of the papilla of Vater. Pneumonia complicated the postoperative course. On May 3, the blood diastase was 39. On May 13, following recovery from the infection, the blood diastase was 160. In this case there undoubtedly was the complicating factor of a partial obstruction of the pancreatic duct, which probably contributed to the rise of diastase to the higher level observed.

The presence of infection, in itself, apparently does not cause a decrease in the blood diastase, especially if there is no absorption from the infected focus. The slough of a large tumor or the trauma accompanying extensive resections in several cases coincided with diminished

blood diastase, but the decreased values were not marked. Decreases observed immediately after surgical intervention probably fall into this class.

By far the most significant cause of decreased blood diastase in this series of cases is, in our opinion, the debilitating effect of the progress of the disease on the patient. This cannot be said to be due to cachexia, which is a pronounced terminal factor in some of the cases, for the lowest diastase values were observed in noncachectic persons, while cachectic patients were observed with only moderate depressions of the diastase. Fever and infection, as causes, have been ruled out. Manzini [7] claimed that the blood diastase rapidly decreased at death, yet we have observed normal values for blood diastase shortly prior to death; in some instances these values were obtained in samples of blood examined within twenty-four hours before the patients died. There remains, therefore, some "toxic" effect of the disease, not necessarily observed in all cases of cancer, which, when present, usually is progressive with

TABLE 2.—*Fate of Patients with Normal, Low and High Blood Diastase*

	Normal Blood Diastase	Low Blood Diastase	High Blood Diastase
Deaths	10*	7	4
Condition unfavorable	17	9	1
Condition good	14	5	0
Condition unknown	13	1	0
Total	54	22	5

* Three of these cases, with normal blood diastase at first, showed a definite decrease in blood diastase at a later determination.

the disease. In our series of cases analysis shows an unfavorable prognosis in more of the cases with low or persistently low values for blood diastase than in cases with normal values. Table 2 summarizes the cases with respect to the fate of the patients.

The following cases are examples of malignant disease with low blood diastase.

CASE 7.—A woman, aged 53, had a sarcoma of the uterus, which was confirmed by laparotomy on Sept. 1, 1932. High voltage roentgen therapy was given from September 23 to October 15, inclusive. On September 26, the blood diastase was 71, and on November 5, 17. The patient died on December 5.

CASE 8.—A woman, aged 50, had undergone radical resection of the breast for adenocarcinoma three years previously. The present diagnosis was adenocarcinoma en cuirasse of the chest, abdomen, breast, leg and arm; the nutrition was good. On Oct. 15, 1932, the blood diastase was 16. She died on October 29.

CASE 9.—A woman, aged 56, underwent cholecystectomy for carcinoma of the gallbladder on May 11, 1932. Metastatic nodules were present in the liver. On Jan. 12, 1933, the blood diastase was 23; on January 31, 22, and on February 1, 22.

7. Manzini, quoted in Oppenheimer, Carl: Die Fermente und ihre Wirkungen, ed. 5, Leipzig, F. C. W. Vogel, 1925, vol. 1, p. 731.

Normal Blood Diastase.—In fifty-four patients, or two thirds of all those studied, a normal level of the blood diastase was observed at the first examination. Ten of these patients died. In three of the ten who died the blood diastase definitely decreased prior to death; three patients who died shortly after operation were in good general condition with a normal amount of blood diastase until just before death; in three patients who were discharged from the hospital, no further opportunity for study was available during the long course of the disease, while in the last patient the level of the blood diastase was normal prior to death, which was due to the effect of widespread hepatic metastasis. Fourteen patients, or 26 per cent of those with normal levels of the blood diastase, are still in good condition, free from evidence of return of the disease. Seventeen patients are in an unfavorable condition, the prognosis being poor, but they are unavailable for determinations of diastase at present. It would be interesting to study the levels of the blood diastase in these two groups to see whether there is a maintenance of the diastase level in the former group and a fall in the latter. The few cases that have been sufficiently studied to date suggest that this is a probability. The fate of the remaining thirteen patients is unknown.

Case 10.—A man, aged 42, underwent resection of the ileum for medullary carcinoma in 1925. Abdominal pain, a tumor and loss of weight were present in April, 1932. On March 26, 1932, the blood diastase was 190; on May 5, 72, and on May 7, 84. Exploratory laparotomy, performed on May 7, revealed a retroperitoneal mass obstructing the common bile duct. The course of the disease was progressive. On November 5, the blood diastase was 26, and on November 7, 31. (There was a progressive decrease in blood diastase.)

Case 11.—A man, aged 68, had a carcinoma of the lung. On May 6, 1932, the diastase was 100 and on July 1, 76. The patient was cachectic. He died on July 4. (There was a progressive decrease in blood diastase.)

Case 12.—A man, aged 58, had a carcinoma of the pancreas. On March 12, 1932, the diastase was 125; on April 9, 94, and on April 13, 78. He died on June 18. (There was a progressive decrease in blood diastase.)

Case 13.—A woman, aged 38, had an adenocarcinoma of the breast, graded 4. On June 20, 1932, the blood diastase was 123. Resection of the breast was performed on July 1. On July 15, the blood diastase was 128. High voltage roentgen therapy was given on September 1, 5 and 9. On November 8, the blood diastase was 108. The general condition was good, with no evidence of recurrence. (The level of the blood diastase remained constant.)

EFFECTS OF TREATMENT ON THE BLOOD DIASTASE

Surgical Intervention.—It may be said that the influence of surgical intervention on the blood diastase of patients with cancer is indirect, exerted chiefly through its effect on the general condition of the patient. Removal of ulcerating lesions, with consequent beneficial effects on the patient, was observed in some instances to be accompanied by a change from a low to a normal level of the blood diastase.

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CASE 14.—A man, aged 55, had a squamous cell carcinoma of the jaw. On May 1, 1932, the blood diastase was 64. Radical resection of the jaw was performed on May 14. On May 23, the blood diastase was 188, and on May 27, 183, an increase of about 200 per cent. The general condition was good.

In one case, the temporary beneficial effects of laparotomy on a metastatic malignant tumor of the liver was followed by a temporary increase in diastase from a low to a normal level.

Postoperative infections and, in some cases, the traumatic effects of extensive resections were accompanied by a temporary diminution of the blood diastase.

Radiation.—In discussing the effects of radiation on the blood diastase, the effects of roentgen therapy, radium therapy and implantation of radon seeds will be considered collectively, since our observations are not extensive enough to permit an analysis of the results of each type of therapy independently. We believe that, contrary to the nonspecific effects of surgical intervention on the blood diastase, radiation exerts a definite and specific effect. We have had the opportunity to study twenty-four patients to whom radiation therapy had been applied. Since it was not always possible to see the patients when and as often as we desired, the observations on some were not as extensive as we wished, and the time interval between exposure to radiation and determinations of the diastase varied greatly in individual cases. In most of the cases observed within three or four days after the application of radiation, no change in diastase was demonstrable. In most of the patients who were examined at an interval of a month or more after the application of radiation, the diastase was at a normal level. In seven cases in which a fairly complete series of observations had been made, we were able to record an interesting curve in the blood diastase content, which rose within a week to a level sometimes threefold the original, returning within the following two weeks to the initial level. In one or two cases, a second rise and fall could be observed after a second exposure to radiation, but these did not seem to constitute so striking a response as the first. Seven cases which illustrate the responses to radiation therapy are summarized.

CASE 15.—A woman, aged 34, had a squamous cell carcinoma of the cervix, graded 2. Bleeding had been present since Sept. 19, 1932. There had been a slight loss of weight. The anterior lip of the cervix was infiltrated with hard nodules. There was some infiltration also on the posterior lip, with thickening of the right parametrium. On November 21, the blood diastase was 138. On November 22, 3,125 mg. hrs. of radium exposure was applied to the cervical canal, and an abdominal operation, with the implantation of five radon seeds in the broad ligaments, was performed. On November 28, the blood diastase was 251, and on December 5, 186. High voltage roentgen therapy was applied to the cervix on December 14 and 15, followed by 1,650 mg. hrs. of radium in the cervix on December 16. On December 17, the blood diastase was 126, and on December 19, 154. Six days after the first exposure to radium and radon seeds, there was a

marked increase in the blood diastase. This had fallen, but was still above the initial level a week later. Nineteen days after the treatment with radium, three days subsequent to high voltage roentgen therapy, and while 75 mg. of radium (second exposure) was still in the cervical canal, the blood diastase was at a level identical with the original level. Three days after the second exposure to radium, another rise in the level of the blood diastase was noticeable. The series of determinations ended here, because the patient no longer remained under observation, but the sequence of events indicates the presence of a latent period before the diastase rise is observed and a definite decline toward normal after the maximum of effect has been exerted.

CASE 16.—A woman, aged 55, had a squamous cell carcinoma of the upper jaw, graded 3, of two months' duration when she first came under observation. On July 27, 1932, the blood diastase was 61. On August 6, 2,400 mg. hrs. of radium was applied locally. On August 8, the blood diastase was 261; on August 13, 120, and on November 14, 50. Two days after the exposure to radium, during a marked reaction to the radium, there was a marked increase in the blood diastase. Two months later the blood diastase was below the original level.

CASE 17.—A woman, aged 37, had a squamous cell carcinoma of the cervix, graded 3, of more than one year's duration. It was inoperable. On June 28, 1932, 4,000 mg. hrs. of radium was applied to the cervix. On July 2, the blood diastase was 86. On September 13, the ovaries and iliac nodes were removed. Five gold radon seeds (8 millicuries) were implanted on the posterior aspect of the uterus and on the broad ligaments. On September 17, the blood diastase was 81; on September 24, 264; on October 15, 108, and on November 26, 101.

On two occasions in this patient, four days after exposure to radium or radon, no apparent change from normal could be detected in the blood diastase. However, eleven days after the implantation of radon seeds there was a marked increase in the diastase, which gradually fell to the original level in the following two months.

CASE 18.—A man, aged 60, had a carcinoma of the left tonsil of from six to seven weeks' duration. On Dec. 17, 1932, the blood diastase was 72. Twelve radon seeds were implanted in the tonsillar fossa on the same day. On December 27, the blood diastase was 104; on Jan. 3, 1933, it was 120. Ten days following implantation of the radon seeds there was a definite rise in the level of the blood diastase, which continued to rise the following week.

CASE 19.—A man, aged 55, had a carcinoma of the left anterior glossopharyngeal fold. On Dec. 24, 1932, the blood diastase was 121. On December 28, implantation of twelve radon seeds in the fauces was made. On December 30, the blood diastase was 163, and on Jan. 2, 1933, 97. A rise two days after the implantation of radon, with a return to normal two days later, was observed.

CASE 20.—A woman, aged 61, had a carcinoma of the right breast en cuirasse, with pleural effusion, of eight months' duration. On Oct. 22, 1932, the blood diastase was 64, and on November 4, 49. On November 18, high voltage roentgen therapy was applied. On November 21, the blood diastase was 118. High voltage roentgen therapy was given on November 22 and 25. On November 26, the blood diastase was 75, and on November 28, 71. Three days after the first exposure to high voltage roentgen therapy there was a rise in the blood diastase. In spite of continued roentgen therapy, the diastase level fell subsequently, but remained somewhat higher than the original levels.

CASE 21.—A man, aged 63, had a squamous cell carcinoma of the tonsil, graded 3, of one year's duration. On Oct. 17, 1932, the blood diastase was 108. On October 19, eighteen radon seeds were implanted in the tonsillar fossa. On December 15, the blood diastase was 188, and on February 1, 132.

It is evident from the cases cited that the increase in blood diastase does not appear in all cases in the identical period of time, nor does the high level persist for equal lengths of time. This difference may depend on (1) the site of the exposure, (2) the type of exposure (i. e., roentgen, radium or radon seeds) and (3) the dosage. Whether the rise in the diastase occurs only in cases of cancer, or in healthy persons also, has not been determined. Caspari [8] and others described the general systemic effects of roentgen therapy, even when the exposure was to a local region. Caspari observed, for example, an increasing leukocytosis within two weeks after roentgen exposure, with a gradual return of the leukocyte count to normal in the following few weeks. The behavior of the blood diastase in its response to radiation may be a part of a general enzyme activation as a result of irradiation.

SUMMARY

Eighty-one cases of malignant disease were investigated to determine the diastase content of the blood at various times during the course of the illness. Marked fluctuations of the diastase level in individual patients could be observed at different times. Twenty-two of the patients had low blood diastase when first examined. Five of the patients with low diastase subsequently had a normal diastase value. Sixteen patients, or 78 per cent of those with low diastase, died, or were in an unfavorable state of health. Fifty-four patients were found to have a normal content of diastase in the blood when they were first examined. Eight subsequently had low blood diastase. About one half of the patients with normal content of diastase in the blood subsequently died or were in an unsatisfactory state of health at the time this report was written. Five patients had high blood diastase. Two of them had obstruction of the pancreatic duct, and in two the determinations were made shortly after radiation therapy. All of these patients had died or were hopelessly ill subsequent to the time they were studied.

A definite increase in the blood diastase was observed shortly after radiation therapy. This increase followed a latent period of some days during which no noticeable change in the diastase content of the blood could be detected. After an interval of from one to four weeks, the blood diastase became normal in amount. Further study of this phenomenon is necessary.

CONCLUSION

As a diagnostic test for cancer, the determination of the blood diastase is not significant. Its value as a prognostic test has not as yet been conclusively estimated; this will require further observation of the cases studied.

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8. Caspari, quoted in Rahm, H.: Die Röntgentherapie des Chirurgen, Neue deutsche Chirurgie, Stuttgart, Ferdinand Enke, 1927, vol. 37, p. 306.

CELL-PLASMA RATIO AND ESTIMATIONS OF HEMOGLOBIN BY CELL CONCENTRATION

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It has long been recognized that marked variations occur in the plasma content of the blood both in health and in disease. The average value of the plasma in the blood of a healthy person under basal conditions is about 50 per cent, with a cell-plasma ratio of approximately 1. In disease, the prime factor is hydremia, often associated with primary renal disease or circulatory failure. Here there is a relative increase in the plasma content and therefore a cell-plasma ratio of much less than 1. Indirectly, there is also a relative increase in the plasma in primary anemia and in most secondary anemias, owing to a paucity of cellular elements, with a consequent low cell-plasma ratio.

METHOD OF DETERMINING CELL-PLASMA RATIO

The method for determining the cell-plasma ratio has been reported in detail by Felsen.[1] Briefly, capillary blood is taken by means of a tube approximately 10 cm. in length and from 1 to 2 mm. in inside diameter, containing a little powdered sodium citrate as an anticoagulant. The tube is centrifugated until the maximum cell packing has been obtained. The clearly defined cell and plasma layers are then measured.

With this method, the cell-plasma ratio was determined for the same patient at five different times during the day. There was a great variation in the proportion of plasma to cells in different subjects. This was most marked within the first half hour after the ingestion of large amounts of fluid (table 1).

METHOD OF ESTIMATING HEMOGLOBIN

As the difference in the relative amount of plasma and therefore in the concentration of erythrocytes is apparent, it can readily be understood why the present methods of estimating the hemoglobin colorimetrically are subject to error aside from the usual technical difficulties. Under ideal conditions, the estimations of the hemoglobin content of the blood of the same patient not infrequently varied 10 per cent on the same day. This was always due to a change in the relative dilution of the erythrocytes by plasma.

From the Pathological Department, the Bronx Hospital.

1. Felsen, Joseph: Arch. Path. **8**:269, 1929.

With these observations in mind, Felsen [2] devised a method for the determination of the hemoglobin content directly on centrifugated cells undiluted by plasma. The method is the same as that described for determining the cell-plasma ratio, except that the cell column is separated from the plasma by cutting the capillary tube at their junction. The Sahli pipet is applied directly to the cut end of the blood column, and the cells are sucked up to the 10 c. mm. mark. The percentage of hemoglobin is determined by the usual Sahli method.

CORRELATION OF VALUES FOUND FOR HEMOGLOBIN BY OLD AND NEW METHODS WITH CELL-PLASMA RATIOS

The cell-plasma ratios were determined and the hemoglobin percentages estimated by the old and new methods for a series of one hundred patients in the wards of the Bronx Hospital. The correlation

TABLE 1.—*Variations in the Cell-Plasma Ratio During the Day in the Same Patient*

		Cell-Plasma Ratio				
Date	Diagnosis	Before Breakfast	One-Half Hour After Breakfast	11 A. M.	1 P. M.	3:30 P. M.
12/ 6/33	Diabetes	0.74	0.48	0.73	0.66	....
1/17/33	Grip	0.73	0.63	....	0.66	0.64
1/19/33	Diabetes	0.68	0.41	....	0.71	0.46
1/23/33	Arteriosclerotic heart disease	0.73	0.50	....	0.85	0.72
1/25/33	Post partum	0.74	0.52	....	0.64	0.60
2/ 1/33	Normal	0.80	0.46	....	0.72	0.60

studies were made on blood taken before and one-half hour after the ingestion of from 500 to 750 cc. of water.

When the cell-plasma ratio approximated 1, the values obtained for hemoglobin by the old and new methods were identical. When the cell-plasma ratio was low, the new method gave a considerably higher percentage of hemoglobin than the old method (table 2). The values obtained by the cell concentration method were uniform at different times of the day regardless of the factors affecting the dilution of the blood.

The discrepancy in the values for the hemoglobin of whole blood before and after meals as determined by the old method was greatest when the variation in the cell-plasma ratio was greatest. In table 2, group 1 shows forty-two cases (42 per cent of the patients studied) with variations of 10 per cent or more.

When the variations in the cell-plasma ratio were negligible before and after the intake of fluid, the percentage of hemoglobin determined by the old method likewise remained about the same. The failure of

2. Felsen, Joseph: Arch. Path. **8**:484, 1929.

TABLE 2.—*Results in One Hundred Patients Examined*

Case	Diagnosis	During Fasting: Cell-Plasma Ratio	During Fasting: Hemoglobin Percentage: Old Method	During Fasting: Hemoglobin Percentage: New Method	After Ingestion of Water: Cell-Plasma Ratio	After Ingestion of Water: Hemoglobin Percentage: Old Method	After Ingestion of Water: Hemoglobin Percentage: New Method	Variations in Cell-Plasma Ratio	Variations in Hemoglobin Percentage (Old Method)
	Group 1: Variations in Hemoglobin (Old) of 10 per Cent or More								
2	Normal	0.70	90	95	0.70	80	96	0.00	10
4	Bronchopneumonia	0.80	65	70	0.52	55	70	0.28	10
5	Fissure in anus	0.91	90	90	0.75	80	90	0.16	10
15	Cerebral thrombosis	0.90	70	75	0.65	60	75	0.25	10
16	Diabetes	0.84	82	85	0.70	70	84	0.14	12
17	Diabetes	0.77	80	80	0.60	70	82	0.17	10
18	Prostatitis	0.82	75	80	0.60	64	80	0.22	11
19	Post partum	0.81	75	80	0.50	65	80	0.31	10
20	Post partum	0.90	75	82	0.50	65	80	0.40	10
26	Prenatal	0.80	90	95	0.52	80	95	0.28	10
31	Prenatal	0.90	80	83	0.42	70	83	0.48	10
32	Post partum	0.53	60	96	0.43	49	106	0.10	11
33	Post partum	0.69	62	84	0.52	50	85	0.17	12
38	Post partum	0.80	75	80	0.32	60	81	0.48	15
40	Post partum	0.90	78	82	0.40	60	82	0.50	18
41	Normal	0.72	80	85	0.53	70	86	0.19	10
42	Normal	0.52	60	95	0.41	49	96	0.11	11
45	Pulmonary abscess	0.70	60	80	0.40	50	80	0.30	10
50	Atherosclerosis	0.81	70	80	0.32	60	80	0.49	10
51	Chronic myocarditis	0.72	80	85	0.53	70	86	0.19	10
52	Pyelitis	0.80	65	70	0.52	55	70	0.28	10
54	Diabetes	0.84	82	85	0.70	70	84	0.14	12
55	Grip	0.81	75	80	0.50	65	80	0.31	10
56	Arthritis	0.90	75	82	0.50	65	80	0.40	10
57	? Tuberculosis	0.80	90	95	0.52	80	95	0.28	10
62	Diabetes	0.90	78	82	0.40	60	82	0.50	18
64	Grip	0.90	80	85	0.50	65	84	0.40	15
66	Paratyphoid B	0.75	70	85	0.60	60	85	0.15	10
67	Diabetes	0.77	80	80	0.60	70	82	0.17	10
68	Bronchopneumonia	0.80	65	70	0.52	55	70	0.28	10
69	Diabetes	0.40	60	75	0.30	50	75	0.10	10
72	Arteriosclerotic heart disease	0.70	80	85	0.55	70	85	0.15	10
76	Post partum	0.69	62	84	0.52	50	85	0.17	12
79	Post partum	0.80	75	80	0.32	60	81	0.48	15
80	Fractured rib	0.90	78	82	0.42	60	81	0.48	18
81	Septicemia	0.80	40	50	0.50	30	52	0.30	10
92	Pregnancy	0.80	80	85	0.65	70	85	0.15	10
95	Diabetes	0.60	70	85	0.42	60	85	0.18	10
97	Normal	0.85	75	80	0.70	65	80	0.15	10
98	Normal	0.80	85	90	0.40	70	90	0.40	15
99	Normal	0.82	85	90	0.43	70	90	0.37	15
100	Normal	0.70	90	95	0.50	75	94	0.20	15
	Group 2: Variation in Cell-Plasma Ratio of 0.05 or Less Before and After Meals								
1	Diabetes	0.48	65	86	0.50	60	87	0.02	5
8	Prenatal	0.80	75	80	0.80	70	80	0.00	5
11	Diabetes	0.42	65	85	0.40	65	85	0.02	0
12	Atherosclerosis	0.42	60	78	0.38	58	76	0.04	2
24	Prenatal	0.40	60	91	0.41	57	90	0.01	3
25	Prenatal	0.50	88	100	0.50	88	102	0.00	0
44	Normal	0.70	75	80	0.65	70	90	0.05	5
82	Post partum	0.74	70	75	0.70	65	75	0.04	5
	Group 3: Variation in Cell-Plasma Ratio of 0.3 or More								
19	Post partum	0.81	75	80	0.50	65	80	0.31	10
20	Post partum	0.90	75	82	0.50	65	80	0.40	10
38	Post partum	0.80	75	80	0.32	60	81	0.48	15
40	Post partum	0.90	78	82	0.40	60	82	0.50	18
45	Pulmonary abscess	0.70	60	80	0.40	50	80	0.30	10
50	Atherosclerosis	0.81	70	80	0.32	60	80	0.49	10
55	Grip	0.81	75	80	0.50	65	80	0.31	10
56	Arthritis	0.90	75	82	0.50	65	80	0.40	10
62	Diabetes	0.90	78	82	0.40	60	82	0.50	18
64	Grip	0.90	80	85	0.50	65	84	0.40	15
79	Post partum	0.80	75	80	0.32	60	81	0.48	15
80	Fractured	0.90	78	82	0.42	60	81	0.48	18
81	Septicemia	0.80	40	50	0.50	30	52	0.30	10
86	Normal	0.90	80	85	0.50	75	85	0.40	5
88	Normal	0.84	75	82	0.70	70	80	0.14	5
99	Normal	0.82	85	90	0.43	70	90	0.37	15

the plasma to increase in amount may be due to a delayed absorption of water from the stomach and intestines or to its rapid excretion through the kidneys (group 2). Note that two patients were diabetic.

Group 3 shows the greatest variations in the cell-plasma ratio in sixteen patients, with corresponding changes in the percentage of hemoglobin determined by the old method.

SUMMARY

There is uniformity in the estimations of hemoglobin by the direct method, regardless of diurnal variations in the fluid content of the blood.

The discrepancies in the estimations of the hemoglobin of whole blood by the old method are greatest when the cell-plasma ratio varies the most.

The ingestion of from 500 to 750 cc. of water tends to lower the cell-plasma ratio within the first half hour.

The nearer the cell-plasma ratio approximates 1, the closer is the similarity of the percentages of hemoglobin obtained by the old and by the direct method.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—In the University of Colorado Paul H. Guttman has been appointed assistant professor of pathology, and E. K. Rutledge instructor in pathology.

Gayfree Ellison, professor of epidemiology and public health in the University of Oklahoma, has died at the age of 57.

A. R. Dochez, O. T. Avery and E. F. DuBois have been elected members of the National Academy of Sciences.

The Public Welfare Medal of the National Academy of Sciences was awarded on April 25, 1933, to William H. Park of the New York City Department of Health for his pioneer work and leadership in the application of scientific discovery to the prevention of disease.

Otto Lubarsch has died at the age of 73. A few years ago he was retired from the University of Berlin where he followed Orth in Virchow's chair. In 1931 he published an interesting autobiography (Ein bewegtes Gelehrtenleben. Erinnerungen und Erlebnisse, Kämpfe und Gedanken, Berlin, Julius Springer, 1931), which was reviewed in the ARCHIVES (**13**:541, 1932).

Society News.—The 1933 meeting of the German Pathological Society has been postponed for one year.

The next meeting of the Pathological Society of Great Britain and Ireland will be held at the University of Leeds, July 7 and 8, 1933.

Ella Sachs Plotz Foundation for Advancement of Scientific Investigation.—During the ninth year of this foundation ninety applications for grants were received by the trustees, sixty-five of which came from sixteen different countries in Europe, Asia, South and North America and Australia, the remaining twenty-five coming from the United States. The total number of grants made during this year was thirty-three, one of these being a continued annual grant. Eighteen of the new grants were made to scientists in countries outside of the United States. The secretary is Dr. Joseph C. Aub, 695 Huntington Avenue, Boston.

Blood Donors.—It is reported that an organization to provide blood donors will be worked out for the municipal hospitals in Berlin somewhat after the pattern of the New York plan.

Standards for Pathologists in New York State.—Following the recommendation of the New York State Health Commission, the Public Health Law has been amended to require pathologists in approved laboratories to have certain prescribed educational and technical qualification, including "an adequate knowledge of pathology and, subsequent to graduation, at least four years' training and experience in pathological work . . . of which at least one year shall have been devoted to training and experience in the diagnosis of neoplastic disease."

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

EXPERIMENTAL LIVER DISEASE PRODUCED BY X-RAY IRRADIATION OF THE EXPOSED ORGAN. A. BOLLIGER and K. INGLIS, J. Path. & Bact. **36**:19, 1933.

Experimental disease of the liver is easily produced in the dog by administering a single dose of roentgen rays to the liver after it has been exposed by surgical means. The immediate result of such irradiation with a heavy dose is necrosis of the parenchymatous tissue of the liver, especially near the surface but also deeper in the substance of the organ. If the animal survives the immediate damage to the hepatic parenchyma, death from hepatic insufficiency occurs at a later date—in our series, from five to sixteen months after irradiation. This insufficiency is characterized by jaundice and ascites, and becomes especially manifest within a few weeks of death. The outstanding histologic changes are connective tissue overgrowth of long standing and necrosis of comparatively recent date.

AUTHORS' SUMMARY.

SECRETIN. J. MELLANBY, Proc. Roy. Soc., London, s.B **111**:429, 1932.

The properties of secretin prepared from duodenal mucous membrane were investigated. With the method of preparation described, the yield of secretin was found to be about 10 mg. per five hundred grams of mucous membrane. The product was a white amorphous powder, soluble in water and alkali and insoluble in acid, acetone, ether and chloroform. The preparation had the percentage composition of a protein, and was rapidly destroyed by trypsin. Intravenous injection of 0.02 mg. caused the secretion of about 40 drops of pancreatic juice in the cat. Secretin was also found capable of causing the contraction of intestinal muscle and inducing the secretion of a small amount of bile.

L. E. SHINN.

CORRELATION OF CERTAIN BLOOD DISEASES ON THE HYPOTHESIS OF BONE MARROW DEFICIENCY OR HYPOPLASIA. F. S. LESCHER and D. HUBBLE, Quart. J. Med. **1**:425, 1932.

Purpura hemorrhagica, red cell anemia, agranulocytic angina and aplastic anemia are considered in the light of deficiency diseases. It is suggested that these conditions have a common pathogenesis, in a lack of the essential controlling factor regulating the development of the bone marrow cells from the reticulo-endothelial system. Thus, a lack of control in the production of platelets would result in purpura hemorrhagica. If the erythrocytes were so affected, red cell anemia would result. It is interesting to note that only three cases of red cell anemia were found in the literature. When the production of granulocytes is involved, agranulocytic angina results. If all elements of the bone marrow are defective, aplastic anemia occurs.

N. ENZER.

OSTEITIS DEFORMANS. T. J. O'REILLY and J. RACE, Quart. J. Med. **1**:471, 1932.

The article embraces a review of the literature and an analysis of thirty cases encountered in the course of one year. The average age, when the patient was observed, was 46 years, while the history indicated that the average age of onset was 43. Twenty-four of the patients were males; six, females. Forty per cent of the patients had physical signs of the disease, 33 per cent had symptoms but no physical signs and 27 per cent were without signs or symptoms of the disease.

Twenty-three had a concurrent disease or focal sepsis, such as fibrositis, arthritis or tonsillitis. Seven of the twenty-two patients had a systolic blood pressure over 160. Calcification of the arteries was noted in twelve of twenty-eight cases. There was no evidence of disturbances in the gastro-intestinal tract in this series. One patient had a history of gout. Headache was occasionally present, and was thought to be due to involvement of the skull. Sweating was a prominent symptom. Mental disturbances were not present. Ostearthritis of the hips was present in three cases. Syphilis was not found in any of the cases. No changes were noted in the parathyroid glands, and the glands were removed in two cases without effect. The calcium content of the serum was within normal limits. Inorganic phosphorus was within normal limits. The total nitrogen phosphorus ratio showed variation, but not greater than found in persons without bone dystrophy. There was no impairment of renal function. The blood phosphatase was increased. Likewise there seemed to be a relationship between the phosphatase content of the plasma and the intensity of the symptoms. In some cases it was noted that the urinary calcium was low, and in these there seemed to be increased calcification of the bones. Morphologic examination of the blood showed a slight shift to the left in the leukocytes, but otherwise no significant change. Significant changes in the sedimentation rate were not noted. There was no evidence of urea retention and no significant change of the carbon dioxide content of the blood or the p_H of the plasma. The authors regard the disease as a "reticular" one, primarily involving the reticular cells of the bones. In their opinion it bears a close relationship to the "reticulo-endothelioses," and they consider it analogous to Hodgkin's disease. Arsenic is suggested as a therapeutic measure.

N. ENZER.

MACROCYTIC AND HEMOLYTIC ANEMIA. L. S. P. DAVIDSON, Quart. J. Med. **1**:543, 1932.

A group of cases is reported here in which the outstanding features are anemia with macrocytosis of the red cells, normoblastosis and hyperchromia. Clinically, the differential diagnosis is concerned chiefly with pernicious anemia and acholuric jaundice. Three cases were due to Hodgkin's disease; one case, to lead poisoning. Three cases appeared to be closely related to acholuric jaundice, while in two cases no explanation for the anemia was discovered. The anemia did not respond to liver therapy. Free hydrochloric acid was present in the majority of cases. The spleen was enlarged in all cases.

N. ENZER.

IDIOPATHIC STEATORRHOEA (GEE'S DISEASE). T. I. BENNETT, D. HUNTER and J. M. VAUGHN, Quart. J. Med. **1**:603, 1932.

This is an exhaustive article on so-called celiac disease in adults. Fifteen cases are analyzed. Outstanding observations are the fatty stools, dilatation of the colon, tetany, osteomalacia, anemia, dermatitis and infantilism. Osteoporosis and rickets are often encountered. Glossitis occurs occasionally. Achlorhydria, clubbing of the fingers and opacity of the lens are to be found. Anemia may be hypochromic, hyperchromic-megalocytic or erythroblastic. The blood urea is often below normal; the serum calcium, lowered. There is an increased output of calcium in the stool and occasionally an increase in blood phosphatase. An anatomic background for the disease has not been discovered. It is suggested that the primary disturbance is a failure of gastro-intestinal function. Fifteen cases are reported in detail, and the article is well illustrated.

N. ENZER.

STRUCTURE OF TWO TESTICULAR GRAFTS AFTER A SURVIVAL OF SIX YEARS. E. RETTERER, Ann. d'anat. path. **9**:233, 1932.

Four pieces of a testicle of a young chimpanzee were grafted into a 65 year old man. A marked increase in muscular strength and sexual function developed, and

the patient returned to work. Six years later, weakness reappeared. He again received testicular grafts, and at the operation two of the old grafts were found to have survived. They were removed and examined histologically. The periphery, in contact with a vascular and nutritive supply, was found altered in structure but fairly well intact. The center of each had undergone fatty degeneration. It is concluded that such grafts in contact with nutrition and blood vessels are able to survive and produce an internal secretion. PERRY J. MELNICK.

EXPERIMENTAL HEPATITIS AND CIRRHOSIS PRODUCED BY THORIUM DIOXIDE. RENÉ HUGUENIN, NEMOURS-AUGUSTE and GUY ALBOT, Ann. d'anat. path. **9**:263, 1932.

In order to test the toxicity of thorium dioxide, various amounts were injected into twenty rabbits. Single large doses caused death in a few hours from a severe hepatitis which did not differ from that produced by other poisons. Moderate doses and divided doses given over a long period of time resulted in varying stages of acute to chronic hepatitis—depending on the amount injected—involving both parenchyma and mesenchyma and ending in cirrhosis. In most cases the thorium dioxide was stored by the reticulo-endothelial system, but in some cases there seemed to be an elimination by the biliary tract. Doses equivalent to those recommended as safe for hepatosplenography by Kadrnka and others produced a hepatitis which was perfectly definite but which seemed to decrease in intensity as time went on. These doses also injured liver function, as was demonstrated by the galactose test. When injected into rabbits whose livers were previously abnormal the doses caused death. PERRY J. MELNICK.

DESTRUCTION OF THE LEFT HALF OF THE BUNDLE OF HIS WITHOUT ALTERATIONS OF THE VENTRICULOGRAM. E. GÉRAUDEL, J. GIRARD and J. SIMONIN, Ann. d'anat. path. **9**:715, 1932.

In a 68 year old woman with a Stokes-Adams syndrome and partial heart block, the electrocardiogram showed no evidence of a left bundle branch block. However, autopsy revealed a sclerotic plaque destroying the anterior half of the bundle of His, that part which goes to form the left branch. This was carefully substantiated by serial sections through the entire bundle of His. The question of bundle branch block is considered to be reopened. Immediately after the bifurcation the fibers of the bundle seemed to fuse directly with the myocardium without the intervention of Purkinje fibers. PERRY J. MELNICK.

PHYSIOPATHOLOGY OF ARTERIAL EMBOLI OF THE EXTREMITIES. A. GOSSET, IVAN BERTRAND and JEAN PATEL, Ann. d'anat. path. **9**:841, 1932.

The results of experimental production of emboli were studied in forty dogs. The emboli were introduced into the crural (femoral) arteries by a unique and accurate method. Aseptic and septic emboli were used, and the resulting effects were studied histologically. Four stages were noted: the arrest of the thrombus, the changes in the extremity following arterial obstruction, the changes in the vessels and the resulting thrombosis. Embolectomy and other therapeutic measures are to be discussed in a future article from the point of view developed in this work. PERRY J. MELNICK.

CHANGES IN THE EPITHELIUM OF THE EXPLANTED PAROTID GLAND. W. E. ZYMBAL, Arch. f. exper. Zellforsch. **12**:177, 1932.

In cultures of explanted parotid gland of rabbits and human embryos epithelial structures were observed which were atypical and resembled those seen in mixed tumors of this organ. The epithelial cells showed infiltrative growth closely

resembling that in malignant tumors. The epithelium of the parotid gland shows the same qualities of growth as the derivatives of the epidermal epithelium, and different growth from that of the cells of the gastro-intestinal tract.

WILHELM C. HUEPER.

EFFECT OF PROTHROMBIN AND HEPARIN ON THE PROLIFERATION AND DIFFERENTIATION OF TISSUES IN VITRO. Z. ZAKRZEWSKI, Arch. f. exper. Zellforsch. **13**:152, 1932.

The proliferation and differentiation in vitro and in vivo is regulated by an interaction of prothrombin and antiprothrombin (heparin). Prothrombin acts as a stimulator of growth, while heparin, through its inactivation of prothrombin, inhibits growth. The addition of heparin to plasma therefore favors differentiation and enables the growth of tissues in a medium in which the possibility of an assimilation of food substances is restricted (blood plasma and serum) by a decrease of the proliferative activity.

WILHELM C. HUEPER.

THE GROWTH OF TISSUE CULTURES IN IMMUNE SERUM. KARL FELLINGER, Arch. f. exper. Zellforsch. **13**:310, 1932.

Serum from rabbits given injections of pulp of embryonic chicken heart showed a definite cytotoxic action on fibroblasts and epithelial cells explanted in it. The degree of inhibition of growth depended on the concentration of the serum used. There was no evidence of cell-specific action of the serum.

WILHELM C. HUEPER.

WATER METABOLISM IN PULMONARY TUBERCULOSIS. M. KERESZTES, Beitr. z. Klin. d. Tuberk. **80**:569, 1932.

In pulmonary tuberculosis, retention of water occurs without the production of noticeable edema. The cause of this is not a disturbance of the circulation but faulty metabolism. Water retention is more likely to occur in exudative malignant types of the disease.

MAX PINNER.

THE METABOLISM OF TUBERCULOUS PATIENTS AND THE INFLUENCE OF NUTRITION. F. STRIECK and A. URRA, Beitr. z. Klin. d. Tuberk. **85**:85, 1932.

The metabolism is usually increased in pulmonary tuberculosis. An increase and decrease of the basal metabolic rate frequently precede clinical improvement or deterioration. In patients on a salt-free diet, the basal metabolism usually decreases without definite clinical improvement. Alkali reserve and alveolar carbon dioxide tension are not influenced by this diet. Hepatic function in the levulose test is normal. A theoretical reason for the limitation of protein and carbohydrates in the diet of tuberculous patients apparently does not exist.

MAX PINNER.

CHANGES IN THE TEETH AND JAWS IN EXPERIMENTAL SCURVY. W. BAUER, Beitr. z. path. Anat. u. z. allg. Path. **87**:23, 1931.

The dental and mandibular changes in experimental scurvy are attributable entirely to circulatory disturbances and not to disturbance of function of any specific tissue. The injury of the ameloblasts and the secondary changes in the enamel are thus explained. A scorbutic diet for eight days produces hyperemia of the pulp vessels, and the subsequent hemorrhages, odontoblastic injury, cyst formation, spontaneous fractures, loosening of the teeth, alveolar porosis and osteitis fibrosa are all secondary to circulatory changes. The cause of these changes is unknown. Changes in the vessel wall were not found.

W. S. BOIKAN.

Pathologic Anatomy

PATHOLOGIC ANATOMY OF THE EASTERN TYPE OF ROCKY MOUNTAIN SPOTTED FEVER. R. D. LILLIE, Pub. Health Rep. **46**:2840, 1931.

An account of the gross and microscopic pathology of the eastern type of Rocky Mountain spotted fever based on the study of five autopsies is presented. Certain differences between the eastern and western forms of the disease and European typhus may be noted. Bronchopneumonia of greater or less extent is more frequent in the eastern type (in five of the six reported cases, as compared with three of seventeen cases in the western type of the disease). Pneumonia has often been seen in typhus. Fatty changes in the liver seem to have been more frequent in the western type of disease, and splenomegaly appears to have been greater in that form. Scrotal gangrene has not so far been noted in the eastern type in man. Ecchymoses in the serous membranes and renal capsules have not been noted in the eastern form. Meningeal congestion has been more frequently noted in the eastern disease, and focal brain lesions of vascular degenerative and proliferative and focal gliotic characters have been constantly present in the eastern form as contrasted with their almost complete absence in the western type. The eastern type of spotted fever has shown in the brain an arteriolar thrombonecrosis with surrounding infarction which has not been specifically described in European typhus. Further study of the brain in the western type of spotted fever would seem to be indicated.

Vascular and diffuse cellular exudative lesions and focal necroses in the heart muscle have been more often observed in the eastern type of spotted fever than in the western, and the necroses are apparently more frequent than in European typhus. That both the eastern type of spotted fever and typhus give rise to lesions of the vasa vasorum of the aorta seems to be indicated, while the few cases of the western type of spotted fever in which the aorta has been studied have not shown such changes.

Capillary and sinus thrombosis and focal necroses in the liver and spleen have been noted in both varieties of spotted fever and seem to be more frequent than in European typhus, while reticulum cell swelling occurs in both diseases, with phagocytosis of erythrocytes more prominent in typhus. The reticulum cell-macrophage reaction in lymph nodes appears to have been more prominent in spotted fever than in typhus, and in the eastern type of spotted fever may go on to necrosis, as in typhoid. The changes in the suprarenals have been slight but fairly similar in character in typhus and spotted fever.

The focal vascular and cellular exudative reaction observed in the kidneys in the eastern type of spotted fever has occurred more often than in the western type, and the endovascular proliferation, degeneration and thrombosis seem more prominent than those reported in European typhus. The occurrence of focal exudative, hemorrhagic and vascular lesions in the juvenile testis in the eastern type of spotted fever contrasts with the absence of these lesions in the western variety, but in the cases of that type reported in males the patients have nearly all been adults. Similar vascular and cellular exudative lesions, but not hemorrhages or vascular necroses, are reported in European typhus.

Cutaneous hemorrhage seems to have been more prominent in the western type of spotted fever than in the eastern, in accord probably with its more acutely fatal course, and thrombonecrotic vascular changes were also relatively less frequent in the eastern type. Changes seen in the typhus exanthem seem also to have been more acute and severe than in the eastern type of spotted fever, but the more frequent vascular necroses, with medical involvement of larger vessels, of the western type of spotted fever are, according to Wolbach, Todd and Palfrey, less prominent or absent in typhus. AUTHOR'S SUMMARY.

TUBERCULOSIS OF SYSTEMIC ARTERIES WITH FATAL RUPTURE. H. L. SHEEHAN and R. WHITEHEAD, J. Path. & Bact. **35**:733, 1932.

Thirty-one cases of aneurysm and rupture of tuberculous systemic arteries are classified, including the two new cases here reported. In one of these the sub-

clavian artery, and in the other a branch of the splenic artery, was affected by tuberculosis and had ruptured with fatal results. AUTHORS' SUMMARY.

CLUMPS OF ASBESTOSIS BODIES IN THE SPUTUM OF ASBESTOS WORKERS. M. J. STEWART, N. TATTERSALL and A. C. HADDOW, J. Path. & Bact. **35**:737, 1932.

While individual asbestosis bodies in large or small numbers are present in the sputum of the vast majority of workers with asbestos, clumps of bodies are encountered only on rare occasions. Their presence points to disintegration of pulmonary tissue and is therefore of far greater significance than the finding of single bodies, however numerous. It may be compared with the presence of elastic tissue in the sputum in phthisis. AUTHORS' SUMMARY.

SOME OBSERVATIONS ON THE EOSINOPHILE CELL. J. H. BIGGART, J. Path. & Bact. **35**:799, 1932.

The eosinophil cell of the tissues is an emigrated eosinophilic leukocyte. Local eosinophilia occurs at the expense of the circulating eosinophils. It may persist after the disappearance of the general eosinophilia. It can be experimentally reproduced by injections of protein and peptone in guinea-pigs. Amino-acids are without effect. The eosinophilic infiltration is removed via the lymphatics. It is suggested that the local eosinophilia of pathologic tissues is due to the presence of protein in the infiltrated area. General eosinophilia can be produced by repeated injections of protein. Egg albumin also produces a general basophilia. General eosinophilia is accompanied by an eosinophilic infiltration of the spleen and by an eosinophilic reaction of the marrow. The eosinophil is formed in the marrow and in adult life in the marrow alone except in cases of dyscrasias of the blood with myeloid metaplasia in other organs. AUTHOR'S SUMMARY.

POLYCYSTIC DISEASE OF THE LUNGS. A. P. DUSTIN, Arch. de biol. **42**:229, 1931.

A male infant, aged 9 months, suffered from coughing, vomiting, cyanosis and dyspnea, and died from suffocation coincidental with bronchopneumonia. At autopsy, both lungs were riddled with thin-walled vesicles from 1 to 20 mm. in diameter, which contained air or thin fluid. They were closely crowded together in the upper lobes immediately beneath the uninvolved pleura. Between the cysts were numerous, pale, firm, atelectatic nodules consisting of young fibroblasts and discrete collections of lymphoplasmocytes, into which terminal bronchi had penetrated. The smaller and medium-sized cysts were continuous with the bronchial tree, but the larger ones had so compressed surrounding structures that their bronchial communications had been obliterated. The cysts were lined by large, multinucleated, loosely arranged, syncytial masses separated from each other by irregular spaces. The nuclei numbered up to fifty and varied considerably in size and shape. These giant cells apparently originated from epithelium, as shown by a study of the lining membrane of numerous cysts and their corresponding bronchi. The paper is well illustrated, and a bibliography is appended.

H. L. STEWART.

THE ARGENTOPHILE FIBERS IN MILIARY TUBERCULOSIS. M. B. ARIEL, Beitr. z. Klin. d. Tuberk. **80**:100, 1932.

By impregnation of the reticulum fibers with silver salts they can be demonstrated when they are not revealed by the usual stains. Such preparations show clearly the different reactions of the reticulum, and the author believes that with this method different histogenic types of miliary tubercles can be differentiated, which, however, represent only different phases of essentially the same process.

MAX PINNER.

PAGET'S OSTEITIS DEFORMANS. G. SCHMORL, Virchows Arch. f. path. Anat. **283**:694, 1932.

In 1926, Schmorl expressed the opinion, which was in accord with the then prevailing view, that Paget's osteitis deformans and von Recklinghausen's generalized osteitis fibrosa are phases of the same disease. In 1930, as the result of study of a much larger material, he announced the belief that the diseases have nothing in common. This conception, which forms the basis of the present profusely illustrated and detailed histologic description of osteitis deformans, is based on 190 cases of Paget's disease, 138 of which Schmorl collected between March, 1926, and the end of 1930 in the course of examinations of the skeletal system at necropsy. The cases were encountered in a total of 4,614 necropsies of persons over 40 years of age, an incidence of 3 per cent. Schmorl has never seen Paget's disease in a person under 40 years of age. The disease occurred in 3.5 per cent of men over 40 years old who were examined post mortem and in 2.5 per cent of women. The disease was never generalized, although involvement of more than one bone was noted. The chief sites of localization, with the percentages, were: sacrum, 56.5; vertebral column, 50; right femur, 31.2; skull, 28.3; sternum, 23.2; pelvis, 21.7. Histologically characteristic of Paget's disease is the mosaic structure of the involved bone. This picture is due to variously shaped and sized areas of old and new-formed bone separated from each other by a ground substance staining blue with hematoxylin. The blue-stained material is bone undergoing lacunar resorption. Contrary to the opinion of previous investigators and contrary to what occurs in von Recklinghausen's disease, the marrow is normal in the early stages of the disease. Bone resorption and bone formation occur in both spongy and compact bone. Localized areas of fibrosis appear in time in the marrow of the spongy bone; these become transformed into fibrous bone. In the compact bone, the process begins within the central portion with the presence of one or more osteoclasts in the haversian canals. Bone resorption by these cells leads to the formation of spaces in which bone formation and bone resorption proceed rapidly, bone formation usually predominating. During the active stage the bone is incompletely calcified, but may become completely calcified when the process comes to rest. The overproduction of bone is held to be compensatory to the weakening of the bone caused by resorption and by the formation of new bone at such a rate that it cannot be completely calcified before it is in turn partly resorbed. The periosteum may form a layer of dense bone or osteophytic elevations of fibrous bone. The gross and microscopic appearances may be complicated by osteoporosis and bone atrophy, which are not infrequent in elderly patients with Paget's disease. Schmorl has never seen the combination of osteitis deformans with osteomalacia. The cause of the disease is not known. The calcium metabolism appears to be normal; complete calcification of the new-formed bone, as soon as the process of resorption ceases, is evidence that the process is not one of deficient calcium deposition. Schmorl has paid particular attention to the parathyroid bodies in his cases; he has never detected any abnormality in them. A concluding section of the paper gives a concise description of the gross and histologic differences between Paget's osteitis deformans and von Recklinghausen's osteitis fibrosa, which can no longer be considered the hyperostotic and the hypoostotic forms of a single disease for which Christeller proposed the name osteodystrophia fibrosa.

O. T. SCHULTZ.

SKELETAL CHANGES IN A CASE OF OSTEOGENESIS IMPERFECTA. A. WILTON, Virchows Arch. f. path. Anat. **283**:778, 1932.

The condition reported occurred in a child that lived to the age of 3 years. The short stature and deformities and the roentgenographic, gross and microscopic changes in the bones were such as are characteristic of osteogenesis imperfecta. The histologic findings in the bones were similar to those that the author has previously described in experimental scurvy due to lack of vitamin C. As a working hypothesis to explain a variety of diseases that are characterized by abnormalities in the development, formation and resorption of bone, Wilton postulates

that the supporting tissues in their syncytial and indifferent stage require for normal development and differentiation not only the materials necessary for the formation of energy and of living tissue, but also small quantities of substances that act as biocatalyzers. Of great importance as biocatalyzers are the vitamins and hormones. Some of these influence more especially the activities of the plasma; these are plasma catalyzers. Others influence the nuclear activities and are nuclear catalyzers. Vitamin C is a plasma catalyzer; vitamin D and the parathyroid hormone are nuclear catalyzers. Osteogenesis imperfecta, osteogenesis imperfecta tarda, and osteopsathyrosis idiopathica are diseases caused by a deficiency in or absence of plasma catalyzers.

RENAL CHANGES IN MIXED DIPHTHERITIC AND SCARLATINAL INFECTION. R. STANKIEVITEZ, Virchows Arch. f. path. Anat. **284**:1, 1932.

Stankievitez studied the kidneys in thirty fatal cases of mixed diphtheritic and scarlatinal infection epidemic in Estonia in 1926-1927, and 1928-1929. He classifies the main types of lesions as nephrosis, glomerulonephrosis, acute diffuse nephritis and glomerulonephritis. Nephrosis he ascribes to the action of diphtheria toxin on the tubular epithelium. Diphtheria alone does not cause glomerulonephrosis; this lesion must be due to the combined action of the two toxins. Diffuse infiltrative nephritis, which he calls nephritis lymphatica acuta, and which he considers an early stage of the renal changes caused by scarlet fever, occurs early in the disease and is due to the exotoxin of the scarlatinal streptococcus. Glomerulonephritis is caused by the streptococcus and its endotoxin. Mixed forms of renal involvement resulted from the combination of the different toxic factors in varying proportions, and in part from the degree of immunity developed.

O. T. SCHULTZ.

RELATION OF ABNORMALITIES OF THE BODY OF THE SPHENOID BONE TO THE ADIPOSOGENITAL SYNDROME. J. SOÓS, Virchows Arch. f. path. Anat. **284**:49, 1932.

Soós presents and discusses cases of obesity and of Fröhlich's syndrome that he ascribes to abnormality or exostosis of the dorsum sellae or posterior clinoid processes of the sphenoid bone. The abnormalities described exert their effect through pressure on the region of the floor of the third ventricle. Postencephalitic and hypophyseal forms of the adiposogenital syndrome are recognized. He thinks it is necessary to recognize also an osteogenic form.

O. T. SCHULTZ.

ACUTE ENDOCARDITIS OF THE PULMONIC VALVE. H. OELMEYER, Virchows Arch. f. path. Anat. **284**:120, 1932.

Oelmeyer reports a case of acute vegetative endocarditis of the pulmonic valve. None of the other valves was involved. The patient was a youth 17 years old, in whom acute purulent tonsillitis led to staphylococcic bacteremia. In the 2,875 necropsies performed from 1926 to 1931 in the hospital from which the report comes, there were only two other cases of pulmonic endocarditis.

O. T. SCHULTZ.

PRIMARY SCLEROSIS AND OBLITERATIVE ENDARTERITIS OF THE PULMONARY ARTERY. H. BREDT, Virchows Arch. f. path. Anat. **284**:126, 1932.

Bredt presents a study of the pulmonary vessels in three cases of the same type of severe pulmonary arterial disease. The patients were respectively 40, 33 and 53 years old; the youngest was a man; the others, women. The clinical course was that of cardiac decompensation of rather sudden onset, with relatively short duration and no increase in blood pressure, and with enlargement of the heart to the right. Anatomically there were marked hypertrophy and dilatation of the right side of the heart, with sclerosis of the larger branches of the pulmonary artery, but not of a degree sufficient to account for the cardiac hypertrophy. Histologically there was severe disease of the smaller branches of the pulmonary

artery, the process being most marked in vessels less than 0.25 mm. in diameter. The medium-sized arteries revealed areas of medial degeneration, with destruction of muscle fibers, rupture of elastic fibrils and necrosis. The intima had proliferated over such areas. In the smallest vessels, diffuse intimal proliferation had led to extreme narrowing, and even complete obliteration, of the lumen. The adventitia was not involved. In the case with the most marked lesions, hemorrhage into the walls of the thickened arterioles had been followed by canalization of the wall and endothelialization of the spaces; there were miliary aneurysms, and the thick walls of some of the arterioles were completely necrotic. Bredt considers the medial degeneration the primary process, and the intimal proliferation secondary. One may question whether the widespread obliterative endarteriolitis was not primary, and the medial change of the vessels of larger caliber secondary to this process. Bredt retains the name primary pulmonary arteriosclerosis for the condition described, but suggests arteriopathia pulmonalis idiogenica as a better designation for the various forms of arterial disease limited to the pulmonary artery. The clinical course and the histogenesis lead Bredt to believe that the disease is due to the action of an unknown specific toxin.

O. T. SCHULTZ.

UREMIC ULCERATION AND NECROSIS OF THE GASTRO-INTESTINAL TRACT. W. WÜRTH, Virchows Arch. f. path. Anat. **284**:175, 1932.

Würth made a study of the ulcers and necroses of the gastro-intestinal tract in cases of fatal uremia to test the correctness of Siegmund's theory that such lesions are the result of arteriosclerotic changes in the small vessels of the submucosa. In one case with multiple small ulcers of the stomach, the arteriolar changes described by Siegmund were seen in the vessels at the base of the ulcers. In two cases with multiple early necroses of the tract, no vascular involvement was noted. Although the gastro-intestinal lesions of uremia may be due to arteriosclerosis of the small vessels in some instances, in the majority of cases the older theory of the toxic action of products derived from the breakdown of urea excreted into the intestine offers the more probable explanation.

O. T. SCHULTZ.

SPREAD OF THE INFLAMMATORY PROCESS WITHIN THE LUNG IN LOBAR PNEUMONIA. H. HEINRICHS, Virchows Arch. f. path. Anat. **284**:187, 1932.

Spread of the inflammatory process in lobar pneumonia occurs in part by the local lymphatics and in part by direct continuity. Aspiration and spread by way of the bronchi are important in the transfer of the process from one lobe to another.

O. T. SCHULTZ.

HISTOLOGY OF ACUTE HOG CHOLERA. H. RÖHRER, Virchows Arch. f. path. Anat. **284**:203, 1932.

In the liver the only changes were toxic parenchymatous swelling and occasionally small round cell infiltration of the interlobular tissue. The kidney revealed tubular parenchymatous degeneration and congestion of the intertubular capillaries. Petechial hemorrhages were seen in the cortex and ecchymoses in the mucosa of the pelvis. If the disease was complicated by secondary bacterial invasion, the renal changes were more marked. In severe uncomplicated infection leading to early death following the administration of the virus for purposes of immunization, multiple small anemic infarcts were noted in the renal cortex. These, like the small infarcts in the spleen, were due to hyaline thrombosis and necrosis of small vessels. Complete necrosis of the renal cortex was seen occasionally; this was due to thrombosis and necrosis of the arcuate arteries.

O. T. SCHULTZ.

Pathologic Chemistry and Physics

CHOLESTEROL OF THE BLOOD PLASMA IN HEPATIC AND BILIARY DISEASES. EMANUEL Z. EPSTEIN, Arch. Int. Med. **50**:203, 1932.

Improvement in the accuracy of diagnosis and prognosis of various hepatic and biliary diseases is possible by means of a quantitative study of the blood cholesterol and cholesterol ester—a simple method requiring only 1 cc. of blood plasma and allowing repeated determinations throughout the course of the ailment. In obstructive jaundice, hypercholesteremia is usually encountered. It roughly parallels the degree of obstruction and the bilirubinemia and returns to normal with relief of the obstruction. Exceptions are noted in cases of marked cachexia, cholemia and superimposed infections. The cholesterol esters in mechanical obstruction rise concomitantly with the total cholesterol in about half the cases; in the other instances they remain normal but lag relatively behind the increased free cholesterol. In degenerative diseases of the liver, a pronounced divergence between the bilirubinemia and the cholesteremia usually occurs; the more severe the damage to the liver, the greater is the tendency to hypocholesteremia. This divergence between the hyperbilirubinemia and the cholesteremia offers a means of differentiation from the cases of mechanical obstruction. In parenchymatous degeneration of the liver, a drop in cholesterol esters parallels the severity of the damage even more accurately. In the rapidly fatal cases, the cholesterol esters are low or absent throughout the course of the disease; in less severe cases, the initial low ester values eventually rise with improvement in the condition. In atrophic cirrhosis of the liver (Laennec), the blood cholesterol remains normal. Variations occur only when hepatitis or degeneration of the liver is superimposed in the terminal stage of the disease. In cholecystitis and cholelithiasis with no obstruction to the biliary outflow, the cholesterol level of the blood is normal or is insignificantly elevated.

AUTHOR'S SUMMARY.

KIDNEY WEIGHT, BODY SIZE AND RENAL FUNCTION. EATON M. MACKAY, Arch. Int. Med. **50**:590, 1932.

In man, renal function, as measured by the ratio of the rate of urinary excretion of urea to the concentration of urea in the blood under certain standard conditions, and kidney weight are both directly proportional to the body surface.

AUTHOR'S SUMMARY.

COPPER IN THE LIVER IN ACUTE YELLOW ATROPHY. A. H. GORDON and I. M. RABINOWITCH, Arch. Int. Med. **51**:143, 1933.

The literature on the metabolism of copper is briefly reviewed, and though the data are not conclusive, they suggest that copper, a normal constituent of food, may be harmful when administered in excess quantities. A case of acute yellow atrophy of the liver is reported in which the liver was found to contain an enormous amount of copper. In spite of the large amount of copper, there was no arsenic. Though it may be difficult to associate the anatomic changes in the liver with the exposure of the patient to copper as long as fifteen years ago, there is a reasonable chemical basis for this association. There is, first, the incontestable fact that the liver contained a large amount of copper—as far as we could ascertain, the largest amount on record. It is suggested that the failure of the liver to excrete the copper may have been due to the fact that copper forms with protein a series of quite stable proteinates. (The blue copper-containing protein of octopus blood, hematocyanine, is an example.) The liver is also rich in products of protein digestion, many of which also form with copper quite stable compounds. This fact is frequently made use of in quantitative analysis. For example, the relative insolubility of the compound formed by copper and aspartic acid serves commonly for the estimation of this acid. The purpose of reporting our case is to prompt further investigation, in view of the present widespread and increasing

use of copper therapeutically. Though copper may have its use, its too general use might do harm. An analogy is suggested in the experiences with the incorporation of iodine in table salt for the prevention of goiter. AUTHORS' SUMMARY.

ETIOLOGY OF GALLSTONES. E. ANDREWS, R. SCHOENHEIMER and L. HRDINA, Arch. Surg. **25**:796, 1932.

Cholesterol is held in solution in bile by the bile salts. A lowering of the bile salt content causes precipitation of cholesterol. Infection of the gallbladder causes rapid absorption of the bile salts, but depresses the rate of absorption of cholesterol. The authors do not consider that gallbladder-mucosal secretion of cholesterol is a factor in the formation of gallstones, as considered by Elman and Graham (*Arch. Surg.* **24**:14, 1932). N. ENZER.

HYPERPROTEINEMIA AS A CAUSE OF AUTOHEMAGGLUTINATION. H. A. REIMANN, J. A. M. A. **99**:1411, 1932.

In a case of myeloma without Bence-Jones proteinuria, the clue to the underlying condition was obtained when it was found impossible to count erythrocytes because of the immediate formation of rouleaux. As a result of this phenomenon, difficulties were encountered in preparing blood smears and in selecting a suitable donor for blood transfusion. Similar phenomena are encountered in other conditions associated with hyperproteinuria, as in pneumonia, kala-azar and pregnancy. Marked hyperproteinuria was present in the case of myeloma he reported. It is suggested that, in this case, disease of the bone marrow may have been largely responsible for the increase in globulin and fibrinogen. AUTHOR'S SUMMARY.

THE COPPER AND NON-HEMOGLOBINOUS IRON CONTENTS OF THE BLOOD SERUM IN DISEASE. ARTHUR LOCKE, E. R. MAIN and D. O. ROSBASH, J. Clin. Investigation **11**:527, 1932.

The iron content of the hemoglobin-free serum of normal persons from whom food had been withheld for twelve hours was found to vary from an average value of 1 ± 15 micrograms per cubic centimeter for young men to a value of 0.77 ± 15 for young women. Values of 1.4 microgram and above were found for the serums of newly born infants, normal adults with mild bilirubinemia, and persons with icterus due to cirrhosis of the liver. Intermediate values were obtained in persons subjected to twenty-four hour fasts, and in pernicious anemia. The increased values of the latter condition became corrected following the administration of liver extract. Normal values were found in carcinoma, pregnancy, hypothyroidism, hyperthyroidism and syphilis. Values approaching 0.4 microgram and less were observed in barbital poisoning, nephritis with edema, conditions involving pituitary and ovarian dysfunction, leukemia, pulmonary tuberculosis and diabetes. The low values of the latter condition were corrected following insulin therapy. Experimental, recoverable depression of the iron level was obtained in rabbits subjected to hemorrhage, carbon monoxide and barbital poisoning, and in horses subjected to injections of the toxins of diphtheria and tetanus.

The copper content of the blood serum of normal persons varied from an average value of 0.8 ± 8 micrograms per cubic centimeter for young men to a value of 0.92 ± 3 for young women. Values of 2 micrograms per cubic centimeter and above were found in pregnancy, at term and in advanced carcinoma. Intermediate values were observed in toxemia, pyrogenic infection, Addison's disease, leukemia, pernicious anemia, cirrhosis of the liver and diabetes. Approximately normal values were obtained in syphilis, nephritis, and conditions associated with a depressed metabolic level, excepting hypothyroidism. Slightly lowered levels were observed in hypothyroidism and polycythemia vera. Markedly lowered levels were manifest in the serum of newly born infants.

The copper-iron ratio was below the normal averages only in conditions involving increased bilirubin in the serum. The ratio was normal in pernicious anemia, hypothyroidism, syphilis and nephritis without edema. In every other condition observed, the ratio was increased, usually to a marked degree.

An analysis of the figures reported has indicated the probable existence of four types of copper-iron picture. The first, found in incipient starvation and in pernicious anemia, may be characterized by slightly increased copper and markedly increased iron, resulting from a "burning out" of the cell catalysts due to a depletion or deficiency in the cell nutrient of substances capable of stabilizing iron in the reduced or ferrous condition. The second, found in carbon monoxide and barbital poisoning and in uncomplicated anemia due to hemorrhage, may be characterized by virtually unchanged copper levels and markedly lowered iron levels, as a result of the retardation in the rate of "burning-out" of the cell catalysts which accompanies a depression of the basal metabolic rate. The third, found in pyrogenic infections, toxemia, leukemia and allied conditions associated with an elevation of the body temperature, may be characterized by increases in copper and decreases in iron proportionate to the general severity of the conditions. The fourth, found in pregnancy, carcinoma and hyperthyroidism, conditions associated with an elevation of the basal metabolic rate without rise in body temperature, may be characterized by markedly raised copper levels without accompanying change in the iron levels.

A careful examination of the copper-iron balance in the serum before, during and after provisional therapy may eventually prove of definite aid in the diagnosis and treatment of disease.

AUTHORS' SUMMARY.

KATAPHORESIS OF INSULIN; THE INSULIN-GLUCOSE REACTION IN VITRO. F. O. HOWITT and E. B. R. PRIDEAUX, Proc. Roy. Soc., London, s. B, **112**:13, 1932.

The electrophoresis of insulin, alone and in the presence of dextrose, was studied over the p_H range from 2.7 to 9.6, colloidal gold being used as an indicator of migration. The iso-electric point of the insulin was approximately p_H 5.4, with an iso-electric p_H range from 4.5 to 6.5 At the p_H of the blood (7.4), no effect of dextrose on the velocity of the migration of insulin was observed. Dextrose appeared to have some effect on the insulin in the p_H region from 8 to 9.5.

L. E. SHINN.

NARCOSIS AND OXIDATIONS OF THE BRAIN. J. H. QUASTEL and A. H. M. WHEATLEY, Proc. Roy. Soc., London, s. B **112**:60, 1932.

A direct correlation is demonstrated between hypnotic activity among narcotics belonging to the same chemical type and capacity to inhibit the oxidation of dextrose, sodium lactate and sodium pyruvate by the brain. The narcotics examined included eight derivatives of the dialkylbarbituric acid series, ethyl carbamate (urethane), chlorbutanol, chloral hydrate, paraldehyde, scopolamine, atropine, morphine, cocaine, nitrous oxide, acetylene, ether and chloroform.

ARTHUR LOCKE.

COMPARISON OF THE BIOLOGIC EFFECTS OF BETA RAYS OF RADIUM AND X-RAYS. OLGA VALENTOVÁ, Ann. d'anat. path. **9**:371, 1932.

The author studied the distribution of calcium and potassium in the skin before and after irradiation by radium and by x-rays. The changes in localization noted were not specific for either, and no difference was noted in their effects. The changes seem to be in the nature of a diminution in vitality or of an aging of the tissues.

PERRY J. MELNICK.

CHEMICAL AND PHYSICAL PROPERTIES OF BONE IN EXPERIMENTAL SCURVY. G. BAYER, Beitr. z. path. Anat. u. z. allg. Path. **87**:204, 1931.

Chemical analysis of scorbutic bones showed an undisturbed percentage composition and total mineral content as compared with normal bones. Nevertheless, the diaphyses of the long bones showed increased fragility. The latter was probably due to osteoporosis.

W. S. BOIKAN.

SIGNIFICANCE OF PLASMA LIPOIDS FOR THE SUSPENSION STABILITY OF THE BLOOD. BOERJE OHLSON and OLLE RUNDQUIST, Biochem. Ztschr. **247**:249, 1932.

The speed of the sedimentation of the erythrocytes in a plasma freed from lipoids without denaturation of proteins does not differ from that in ordinary plasma under normal and pathologic conditions. The plasma lipoids have, therefore, no or only a slight effect on the suspension stability of the blood. The increase in suspension stability which occurs after heating of the normal plasma is not present in lipoid-free plasma.

WILHELM C. HUEPER.

CHOLESTEROL CONTENT OF CARCINOMA LIPOID. R. WILLHEIM and GEORG FUCHS, Biochem. Ztschr. **247**:297, 1932.

The lipoid obtained from washed, healthy carcinoma cells through extraction with absolute alcohol contains a lipoid with a markedly increased cholesterol content in comparison with that obtained from normal parenchymatous organs. The high cholesterol content of malignant tissue is, therefore, not the result of degenerative processes in the malignant cells, but a chemical characteristic. The cholesterol content of embryonic liver does not differ from that of the adult organ. The connective tissue stroma of tumors contains also an increased amount of cholesterol.

WILHELM C. HUEPER.

IODINE CONTENT OF FOOD SUBSTANCES AND INCIDENCE OF GOITER. L. SCHEFFER, Biochem. Ztschr. **247**:418, 1932.

As about 10 per cent of the population of Pecs is affected with goiter, the drinking water and the food substances were examined for their iodine content. It was found that the drinking water and animal and vegetable foodstuffs contain rather high amounts of iodine, so that the daily intake of iodine would be about four times as high as that of the people of La Chaux-de-Fonds, who are not affected by goiter. The theory of iodine deficiency as the cause of goiter is not supported by these investigations.

WILHELM C. HUEPER.

MICRO-IODINE DETERMINATION OF BLOOD. A. WLADYSLAW ELMER, Biochem. Ztschr. **248**:163, 1932.

Five cubic centimeters of oxalated blood is first carbonized and then ashed. The ash is subjected to extraction in the Lacqueur apparatus with 95 per cent alcohol. The extract is colorless. The extract is then evaporated in a gold or platinum dish after addition of potassium carbonate, and after evaporation the residue is heated till an even and pure white precipitate appears. After cooling, from 1 to 2 cc. of 95 per cent alcohol and some water are added and mixed. The resulting salt pulp must be even in consistency. The alcohol extract is decanted into a platinum dish. The extraction is repeated several times. The extract is then evaporated after addition of equal parts of water. The residue is used for iodine determination. This can be done titrimetrically after Winkler or colorimetrically after Reith.

WILHELM C. HUEPER.

RELATION OF CHOLESTEROL TO THE INDOPHENOL-OXYDASE REACTION. I. REMESOW, Virchows Arch. f. path. Anat. **285**:591, 1932.

From test tube experiments with pure cholesterol, the author concludes that the intracellular indophenol-oxydase reaction requires the presence of cholesterol within the cell. In the reaction the cholesterol acts as a catalyzing agent.

O. T. SCHULTZ.

IDENTITY OF CHARCOT-LEYDEN AND BÖTTCHER CRYSTALS. M. BOGEN, Virchows Arch. f. path. Anat. **286**:690, 1932.

The author attempted to determine by crystallographic study whether the Charcot-Leyden crystals of bone marrow, spleen and asthmatic sputum are identical with Böttcher spermine phosphate crystals, as has been claimed by some observers. The Charcot-Leyden crystals were found to have properties identical with those of secondary calcium phosphate crystals prepared by the method of Storm van Leeuwen, but were optically, and therefore chemically, different from Böttcher crystals.

O. T. SCHULTZ.

CONTENT OF NONPROTEIN SULPHUR IN THE FORMED ELEMENTS OF THE BLOOD. N. HAJDU, Ztschr. f. physiol. Chem. **206**:217, 1932.

The nonprotein content of the formed elements of the blood is partly diffusible, partly nondiffusible. The concentration of the nondiffusible portion is about from 4.85 to 5.25 mg. per hundred cubic centimeters of blood. The diffusible fraction corresponds to about 55 per cent of the sulphur content of the plasma. The nondiffusible sulphur can be calculated from the sulphur content of the total blood and that of the plasma.

WILHELM C. HUEPER.

FATS IN DERMOID CYSTS AND THEIR BIOLOGIC SIGNIFICANCE. GEORG BEHMEL, Ztschr. f. physiol. Chem. **208**:62, 1932.

The fats in ovarian dermoids contain large amounts of sterol esters. The saturated esters are present in larger amounts than the unsaturated ones. Ergosterol is probably present. Vitamin A and estrus hormone could not be demonstrated.

WILHELM C. HUEPER.

LIVER AUTOLYSIS. W. LAVES and E. SCHADENDORFF, Ztschr. f. physiol. Chem. **210**:168, 1932.

During autolysis, liver shows a decrease in the electronegative character of the cells, and an increase in the noncoagulable nitrogen and in the aminonitrogen in the extracts running parallel with the degree of histologic change. It is suggested that these chemical and physicochemical methods may be of help in the characterization of "regressive" histologic conditions.

WILHELM C. HUEPER.

ERGOSTEROL AND CALCIFICATION OF THE HUMAN AORTA. RUDOLF SCHOENHEIMER, Ztschr. f. physiol. Chem. **211**:65, 1932.

Ergosterol could not be demonstrated in the ash of arteriosclerotic aortas by spectrophotometric methods or in biologic experiments on vitamin D. Also the cholesterol freed from the unsaponifiable substances, which was thereby 50 times concentrated, did not show, even with large doses, any antirachitic effect.

WILHELM C. HUEPER.

PHOSPHATIDE DEGENERATION OF THE CELLS OF THE BRAIN, LIVER AND SPLEEN IN NIEMANN-PICK'S DISEASE. EMIL EPSTEIN and KARL LORENZ, Ztschr. f. physiol. Chem. **211**:217, 1932.

The chemical examination of the brain, liver and spleen in a case of Niemann-Pick's disease showed that in the process of phosphatide degeneration of cells

not only the unsaturated but also the saturated phosphatides participate to a considerable degree. The phosphatide content of these organs is from eight to ten times the normal. The liver is the organ most affected.

WILHELM C. HUEPER.

ORGANIC PHOSPHORUS COMPOUNDS AND PHOSPHATASE IN THE MAMMARY GLAND. WALTER BORST, Ztschr. f. physiol. Chem. **212**:126, 1932.

The mammary gland contains organic phosphorus compounds. The virginal breast contains the highest amount, the pregnant breast has considerably less, and the lactating breast still less. By far the smallest amounts are found in the senile breast. The tissue of the mammary gland contains a substance with the characteristics of adenosin phosphoric acid. A phosphatase is present in the breast. It is present in increased amounts in the lactating breast.

WILHELM C. HUEPER.

Microbiology and Parasitology

LUNGS OF CHILDREN WITH ASCARIS. A. E. KELLER, H. T. HILLSTROM and R. S. GASS, J. A. M. A. **99**:1249, 1932.

While it is not possible to draw definite conclusions, these observations suggest that in children who are infected with Ascaris lumbricoides and who show no response to tuberculin tests the widening in the hilar areas with increase in the bronchovascular markings is possibly due to the repeated migration of the larvae through the lungs. The changes may occur either as a result of the damage done by the larvae or as the result of infection by micro-organisms which invade the pulmonary tissues at the time the larvae escape from the blood vessels into the alveoli. The changes seen on roentgen examination, which have been attributed to larval migration, are similar to those seen in the childhood type of hilar tuberculosis and may also resemble the changes which occur following repeated nonspecific infections of the lungs.

AUTHORS' SUMMARY.

NEGATIVE OCCULT BLOOD TESTS IN CARRIERS OF ENDAMOEBA HISTOLYTICA. J. ANDREWS and F. ATCHLEY, J. A. M. A. **99**:1340, 1932.

On the basis of the evidence presented in this article, it seems unlikely that E. histolytica is, as has been claimed, an obligatory tissue parasite. That it can and does survive within the lumen of the intestine seems indicated by the high proportion of amebic carriers whose stools give negative tests for occult blood.

AUTHORS' SUMMARY.

DISSOCIATION OF MYCOBACTERIUM LEPRAE. G. B. REED, J. Bact. **24**:357, 1932.

It has been shown that many cultures of Mycobacterium leprae contain two or more types of colony. In a group of fourteen cultures regarded as belonging to the species, part were found to contain only S colonies, part only R colonies and part mixtures of the two together with intermediate forms. Both types have been shown to exhibit a considerable degree of stability on most solid mediums, while both have dissociated in certain culture fluids. S to R dissociation has occurred regularly on a variety of fluid mediums. The R types under all conditions studied have appeared much more stable than the S; yet a sufficient number of instances have been recorded to demonstrate definitely R to S dissociation. The S and R types were also shown to be distinguishable on the basis of habit of growth in fluid mediums and oxidation-reduction potential growth curves, by acid agglutination, by electrophoretic potential and iso-electric points of suspensions and by antigenic content. Antigenic analysis by quantitative complement-fixation and agglutination-adsorption reactions has indicated that the S organisms possess a specific S antigenic substance which is lacking in the R organisms.

AUTHOR'S SUMMARY.

DISSOCIATION AND LIFE CYCLE OF BACILLUS MYCOIDES. I. M. LEWIS, J. Bact. **24**:381, 1932.

Four typical strains have been studied as to dissociation, pleomorphism, filtrability and life cycle. The strains showed minor differences as to colony characteristics but uniformity in morphologic and physiologic characteristics and in the phenomena of dissociation. Dissociation occurred in some but not all of the liquid mediums tested, but not on agar. The rate of dissociation depends on several factors. The most important of these were found to be the temperature of incubation and a culture medium suitable for rapid growth. The rate was generally retarded by depleted mediums, metabolic products, low temperature, inhibitory chemicals and mediums poor in nutrients. The typical colony is unique in form, and any departures however slight may be observed by direct microscopic examination. The characteristic features are adherence to the agar, long parallel filaments of cells which aggregate to form rhizoid-like threads, and a more or less regular spiral symmetry. The chains of cells never form loops or folds but break at a sharp angle. Two series of variants were found to occur in all four strains. These may be designated as adherent and nonadherent. In either case there is progressive orderly variation in one direction. The variants are relatively stable on agar but not in broth. Nonadherent variants failed to revert to the original type, while such reversion occurred in all adherent strains when cultivated on agar. Nonadherence is always correlated with looping rather than with breaking of the threads at sharp angles. All variants and the type strains were found to be similar in morphologic and physiologic characteristics. Pleomorphism is a marked feature in all aged cultures. The variant types of cells are not regarded as specialized reproductive cells, either asexual or sexual. No convincing evidence could be found to support the theory of reproduction by means of gonidia, symplasm or conjugation. This conclusion is based principally on the results of direct examination of the growth in situ. All attempts to obtain growth from the filtrates of liquid cultures resulted in failure. The evidence in favor of a cyclogenic mode of development is mostly negative. Colonial polymorphism is regarded as due to orthogenic variation.

AUTHOR'S SUMMARY.

THE RELATIONSHIP OF STREPTOCOCCUS HEMOLYTICUS TO THE RHEUMATIC PROCESS. A. F. COBURN and R. H. PAULI, J. Exper. Med. **56**:609, 633 and 651, 1932.

The relationship between the incidence of hemolytic streptococci and the geographic distribution of rheumatic fever, the relationship between the recrudescence in the rheumatic subject and infection of the throat with hemolytic streptococci, the development of immune bodies for hemolytic streptococci at the onset of the rheumatic attack and the apparently specific relationship of antistreptocolysin formation to infection with hemolytic streptococci indicate that the infectious agent initiating the rheumatic process is Streptococcus haemolyticus.

FROM AUTHORS' SUMMARY.

THERMAL DEATH TIME OF TREPONEMA PALLIDUM IN VITRO. R. A. BOAK, C. M. CARPENTER and S. L. WARREN, J. Exper. Med. **56**:741, 1932.

The thermal death time of Spirochaeta pallida in extracts from lesions in rabbits' testes was determined in vitro at fever temperatures, the Zinsser-Hopkins and Nichols strains being used. The criteria for the persistence of infectivity of the heated extract were: the development of lesions on inoculation into rabbits, dark-field examination of tissue from the lesions, and the outcome of Wassermann tests of the blood and of reinoculation tests. The two strains of spirochetes had approximately the same thermal death time, although the Nichols strain was somewhat the more resistant. With respect to the latter, five hours at 39 C., three hours at 40 C., two hours at 41 C., and one hour at 41.5 C. were required

to render infective extracts innocuous to other rabbits. The thermal death time of Spirochaeta pallida in testicular extracts in vitro at fever temperatures is so short as to suggest that induced fever may be useful therapeutically in human syphilis.

AUTHORS' SUMMARY.

HEALING OF EXPERIMENTAL SYPHILIS IN RABBITS BY SHORT WAVE FEVER. C. M. CARPENTER, R. A. BOAK and S. L. WARREN, J. Exper. Med. **56**:751, 1932.

Multiple, unsustained fevers (from 41 to 42 C. [105.8 to 107.6 F.]) produced by irradiation in a high frequency electrostatic field (10,000 kilocycles) destroyed Spirochaeta pallida in rabbits with active syphilitic lesions as determined by the injection into normal rabbits of extracts prepared from their testes and popliteal lymph nodes. A single febrile period of six hours at a temperature of from 41.5 to 42 C. was likewise found to be sufficient to destroy Spirochaeta pallida. Infection with Spirochaeta pallida persisted in a control series of untreated rabbits for as long as three hundred and ninety-five days after inoculation, but clinical healing occurred in from three to four months after injection. The interval of time between inoculation and the treatment with fever or between the end of the treatment with fever and reinoculation did not affect the results. The treatment with fever was effective at any stage of experimental syphilis in rabbits.

AUTHORS' SUMMARY.

ISOLATION OF BARTONELLA MURIS. J. MARMORSTON-GOTTESMAN and D. PERLA, J. Exper. Med. **56**:763, 1932.

This organism has been isolated pure on Noguchi's Leptospira medium from the blood of the splenectomized adult rat suffering from bartonella anemia. The organism is a small, actively motile, gram-negative bacillus, which does not produce gas or acid on sugar mediums and does not lake blood in artificial mediums. A severe anemia was produced by injecting cultures of this organism into young rats, rabbits, guinea-pigs and mice, all with intact spleens. A mild anemia was produced in suitable adult splenectomized rats.

FROM AUTHORS' SUMMARY.

THE TRANSMISSION OF NEUROTROPIC YELLOW FEVER VIRUS BY STEGOMYIA MOSQUITOES. N. C. DAVIS, W. LLOYD and M. FROBISHER, JR., J. Exper. Med. **56**:853, 1932.

Encephalitis has been produced both in white mice and in rhesus monkeys by the bites of mosquitoes of the genus Stegomyia carrying neurotropic yellow fever virus. The fixed neurotropic strain of virus cannot be maintained in the mosquito host as well as can the viscerotropic strains. This is doubtless attributable in part to a smaller amount of virus ingested, because of paucity in the blood stream of the mammalian host. These experiments furnish additional evidence that the long-established neurotropic yellow fever virus has changed fundamentally from the parent French strain.

AUTHORS' SUMMARY.

THE CELLULAR REACTIONS TO LIPOID FRACTIONS FROM ACID-FAST BACILLI. K. C. SMITHBURN and F. R. SABIN, J. Exper. Med. **56**:867, 1932.

A comparative study has been made of the cellular reactions induced by phosphatides from five strains of acid-fast bacilli. Each of these reactions is characterized principally by epithelioid cells and giant cells. The phosphatides are first phagocytosed by young connective tissue cells or monocytes. The lipoid is then dispersed into fine particles with the formation of classic epithelioid cells. A comparison has been made of the reactions induced by heat-killed and defatted tubercle

bacilli with those induced by tuberculo-phosphatide. Further studies have been made to determine whether or not the phosphatide causes sensitization to tuberculin. It does not do so. The life cycle of the epithelioid cell has been observed in all its stages.

AUTHORS' SUMMARY.

THE CULTIVATION OF VACCINE VIRUS IN LIFELESS MEDIA. T. M. RIVERS and S. M. WARD, J. Exper. Med. **57**:51, 1933.

No evidence was obtained to indicate that vaccine virus is capable of multiplication in mediums consisting of serum, Tyrode's solution and extracts of tissues. Kendall's K medium is not suitable for the cultivation of vaccine virus.

AUTHORS' SUMMARY.

TOXICITY OF VARIOUS MENINGOCOCCUS PREPARATIONS. C. V. RILEY and M. A. WILSON, J. Immunol. **23**:269, 1932.

Various preparations of meningococci were tested by the Shwartzman method. Those containing the products of cell disintegration were found to be much more toxic than the simple filtrate of culture washings, the most toxic of all being a defatted coccus antigen made by extracting the cells with alcohol and ether and grinding them in a mortar. The reactions obtained with this toxic defatted coccus could be neutralized with homologous immune rabbit serum, but only consistently when the serum was used undiluted and was inoculated intravenously in equal volume with the diluted suspension. The antimeningococcus therapeutic horse serum in 1:10 dilution neutralized the toxic effects of all four of the preparations in Shwartzman's skin sensitivity tests. In the mouse protection tests Murray's endotoxin, unfiltered, was more toxic than the other preparations. High dilutions of the antimeningococcus horse serum protected mice against Shwartzman's toxin filtrate, Murray's endotoxin filtrate and the cellular suspension. High dilutions of the serum did not protect against Murray's endotoxin, unfiltered, or against the defatted coccus. No conclusions have been drawn from these experiments, but the tests indicate that the same toxic substance is present in all of the preparations. The nature of the toxic substance has not been demonstrated by our tests.

AUTHORS' SUMMARY.

ISOLATION AND DIFFERENTIATION OF TUBERCLE BACILLI ON THE BORDET-GENGOU and LÖWENSTEIN MEDIUMS. L. MISHULOW, J. Infect. Dis. **51**:416, 1932.

Bordet-Gengou medium was found excellent for isolation and cultivation of human and bovine types of tubercle bacilli. Twelve strains of tubercle bacilli were isolated from as many human sputums. One strain was isolated from human tissue and three strains from bovine pulmonary tissue. The medium has also been used with great success for the isolation of tubercle bacilli from infected pus. Colonies of the human type could be detected in from twelve to fifteen days (in some instances in from eight to ten days), and of the bovine type in from two to three weeks. Growth of both types could be detected in many instances much sooner than local lesions in inoculated guinea-pigs. The Bordet-Gengou medium, therefore, might be substituted for animals in the isolation of both types. Löwenstein's medium was equally favorable for isolation of the human type of tubercle bacilli, but was entirely unsuitable for isolation of the bovine type, as the latter failed to grow in primary cultures. By using both Bordet-Gengou and Löwenstein mediums, human and bovine types of tubercle bacilli could be differentiated by their growth characteristics. Avian tubercle bacilli grow rapidly and luxuriously on both mediums, giving distinctive rough and smooth colonies. B C G gave such characteristic growth on these mediums that it could be differentiated from typical human and typical bovine strains by the morphologic differences of the colonies. Plating on the Bordet-Gengou and Löwenstein mediums, therefore, may be used as an additional safeguard in preparing B C G vaccine. The Bordet-Gengou medium

is especially advantageous because the glycerin-potato agar can be prepared and stored for many months. The necessary amount can be melted and mixed with sterile blood at the time it is needed, thus giving fresh plates whenever needed.

AUTHOR'S SUMMARY.

A CRITIQUE OF THE SERIAL DILUTION METHOD FOR QUANTITATIVE DETERMINATION OF BACTERIOPHAGE. A. P. KRUEGER, Science **75**:494, 1932.

It is shown, on the basis of earlier experiments relating to the kinetics of the bacteriophage bacterium reaction, that certain factors will operate to produce a considerable error in the serial dilution method for the quantitative determination of phage. Among these factors may be mentioned the initial concentration of bacteria with which the test series is seeded, and the percentage of dead bacteria present in the suspension. The mechanism by which these factors function is detailed in the paper.

A. P. KRUEGER.

THE EVIDENCE OF BRUCELLA ABORTUS INFECTION IN SLAUGHTERHOUSE MEN. J. HENRY DIBLE and M. POWNALL, J. Hyg. **32**:349, 1932.

Men engaged in slaughtering and dressing meat show a higher incidence of Brucella abortus agglutinins than those in similar age and sex groups who are otherwise employed, where titers of 1:20 and upward are observed. This applies especially to men who deal with cattle and sheep; no such increased incidence has been noted in men dealing with pigs. It would seem that a titer in the vicinity of 1:40 serves to indicate evidence of Brucella infection definitely greater than that likely to be found in the generality of the community.

AUTHORS' SUMMARY.

HUMAN TUBERCULOSIS IN RABBITS. LOUIS COBBETT, J. Path. & Bact. **35**:681, 1932.

In rabbits given intraperitoneal injections of tubercle bacilli of the human type there may develop in a few weeks an extensive mild type of tuberculous peritonitis and some degree of miliary tuberculosis in the lungs; occasionally in rabbits that live for several months, severe progressive caseous lesions may form in various organs, particularly the testes and joints and sometimes also the lungs.

SPONTANEOUS INFECTIOUS RHEUMATISM IN MICE. C. LEVADITI, R.-F. SELBIE and R. SCHOEN, Ann. Inst. Pasteur **48**:308, 1932.

The following general summary is given to a study of a streptobacillus, designated as Streptobacillus moniliformis: "The experimental disease up to a certain point shows the etiology and the pathogenesis of certain similar processes in man. . . . It is possible to reproduce . . . polyarthritis, endocarditis, myocarditis, associated with a state of septicemia. . . . Seasonal variations . . . are similar to those of acute articular rheumatism, Bouillaud type."

M. S. MARSHALL

EXPERIMENTAL CEREBROSPINAL MENINGITIS. P. ZDRODOWSKI and E. VORONINE, Ann. Inst. Pasteur **48**:617, 1932.

Suboccipital inoculations of rabbits with types I and II meningococcus regularly produced cerebrospinal meningitis. The authors were also successful in determining a definite lethal dose of organisms. Periodic passages by subarachnoid inoculation during transfers on Dorset's medium resulted in no loss of virulence over a five month period. Young rabbits (from 1,300 to 1,500 Gm.) were found necessary for constant results, and albino rabbits were favored.

M. S. MARSHALL.

"FIÈVRE BOUTONNEUSE." GEORGES BLANC, J. CAMINOPETROS, P. DURAND and J. LAIGRET, Arch. Inst. Pasteur de Tunis **20**:343, 395, 422 and 426, 1932.

1. General Observations (Blanc and Caminopetros): The study considers the clinical aspects (twenty-six case photographs), experimental work and epidemiology of this eruptive febrile disease, noted in Tunis in 1910, and called by Conor and Bruch in 1910 *fièvre boutonneuse*. The disease, relatively recently diagnosed in Greece, has been recognized rarely, in part owing to unfamiliarity with its symptoms. The dog tick, Rhipicephalus sanguineus, in certain districts frequently harbors the virus. Both male and female nymphs were found to be infected, even over winter, and experimental transmission via the egg was shown. The virus passed Chamberland L_2 and L_4 filters, and was not concentrated by centrifugation. The dog was not receptive to the virus, nor were ticks infected from experimentally inoculated dogs. Rabbits, sheep, hogs, pigeons, guinea-pigs and white and gray rats were refractory. The suslik of Macedonia, a rodent (Citillus citillus), was found to be very receptive, and served to maintain the virus. Maintenance of the virus by human transfer was difficult, owing to abortive infections. The virus in man was found in all blood components, and was filtrable as found in serum. The virus was present in blood during all stages of illness; but not after recovery. Convalescent serum was not protective. Immunity existed for at least two months after an attack. The virus in blood, stored on ice, lost its virulence after twelve days.

2. The Weil-Felix Reaction in *"Fièvre Boutonneuse"* (Paul Durand): "Button fever should be alined among those diseases giving constantly a positive Weil-Felix reaction. Unquestionably, in order to secure positive results in all cases, it is necessary to repeat and to prolong examinations, using always at least two strains, 0 x 19 and 0 x 2.

"This infection is thus placed among the diseases: tropical typhus, Rocky Mountain spotted fever, and tsutsugamushi disease, which form a group around exanthematic typhus and its varieties (Brill's disease, Mexican typhus, nautical fever). The Weil-Felix reaction, with strains more or less different from Proteus, appears more and more to belong properly to this group."

3. Marseilles Fever Immunizes Against *"Fièvre Boutonneuse"* (Durand and Laigret): "We have observed that a first attack of button fever of Tunis leaves a complete immunity toward another Tunis virus and that, in the same way, the immunity to the Tunis virus is obtained by an attack of the Marseilles virus. The latter immunity permits us moreover to affirm the identity between the virus of the natural human disease and the virus obtained by inoculation of ticks."

4. Response of Rodents to the Virus of *"Fièvre Boutonneuse"* (Durand and Laigret): A study of the effect of the virus on the gerbil and on the white rat led the authors to postulate the possible presence of a silent infection in animals, perhaps acting as virus reservoirs for ticks. M. S. MARSHALL.

Immunology

AGGLUTININ-FORMATION AFTER ORAL IMMUNIZATION AGAINST TYPHOID AND PARATYPHOID FEVER. ESTHER KRAUSE-SHIMKIN, Zentralbl. f. Bakt. (Abt. 1) **121**:277, 1931.

Forty-six persons were given typhoid-paratyphoid vaccine and ox bile by mouth on three successive days. A quantitative and qualitative analysis of the agglutinins in the serum was made three or four weeks later and compared with the agglutinin types and titers determined before the administration of the vaccines. The object of the study was to test Besredka's postulate that local immunization of the intestine is possible.

The immune serums showed agglutinins in 87 per cent of the persons vaccinated, and 40 per cent averaged a titer of 1:500. The agglutinins were predominantly small flocculating O forms, thus more nearly resembling the forms found in persons

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The immune serums showed agglutinins in 87 per cent of the persons vaccinated, and 40 per cent averaged a titer of 1:500. The agglutinins were predominantly small flocculating O forms, thus more nearly resembling the forms found in persons

ill from typhoid or paratyphoid fever. The maximal titers were higher in persons who had previously been vaccinated or who had recovered from typhoid fever than in those never vaccinated or infected. The serums of the persons vaccinated orally contained O form agglutinins as long as two years after the vaccination.

Vaccination by mouth caused no general or local reactions except for slight nausea in two instances, and none of the vaccinated persons contracted typhoid or paratyphoid fever during the five months after vaccination, although all were workers in a hospital in which thirty-four patients with typhoid fever were treated.

PAUL R. CANNON.

PERCUTANEOUS IMMUNIZATION AGAINST DIPHTHERIA. BUERGERS and F. VON BORMANN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:1, 1932.

In guinea-pigs given subcutaneous injections of anatoxin in quantities corresponding with those employed in man a strong immunity developed. Toxin, anatoxin, extracts of diphtheria bacilli and vaccines rubbed into the skin did not lead to immunization, but it was produced by the rubbing in of proper quantities of anatoxin in the form of salves. There was a marked difference in the efficiency of various batches of salves. Infections of the mucous membranes (conjunctiva and vagina) did not effect local or general immunity in the animal, while subcutaneous injection produced a general as well as a local (mucosal) immunity. Buergers believes that it has not been proved that natural diphtheritic infection in man leads to immunity.

I. DAVIDSOHN.

SPECIFICITY OF ANTIBODIES AGAINST LIPOIDS. E. BERGER and H. SCHOLER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:16, 1932.

Cholesterol was changed into a full antigen by the addition of hog serum, confirming the results of Sachs and Klopstock. The same results were obtained with viosterol. Complement was fixed with the immune serums, but precipitation did not occur. The specificity of the immune serums was tested with a large number of compounds and was found to be very high. Treatment of viosterol with ultraviolet rays changed it into a substance antigenically different from the nonirradiated product. The possibility of applying serologic methods for purposes of chemical identification of lipoids is suggested.

I. DAVIDSOHN.

QUALITIES OF FILTRATES OF GONOCOCCUS CULTURES. I. A. FINKELSTEIN and M. I. TIMOCHINA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:46, 1932.

The authors attempted to decide by animal experimentation whether filtrates of cultures of gonococci possess the qualities of an antivirus as defined by Besredka. The results of the investigation decided the question in the negative sense: Gonococci grew well in filtrates of from two to four day old cultures, less well in filtrates of cultures ten days old and not at all in those of twenty day old cultures. Injections of filtrates under the skin of the scrotum of rabbits did not weaken the toxicity of gonococcus cultures, but acted similarly to them. When filtrates were injected into the peritoneal cavity of mice, the effect was similar to that obtained in the experiments with rabbits. Examination of the peritoneal exudate showed a marked decrease of phagocytosis when mixtures of gonococci and of filtrate were injected. The clinical application of filtrates in gonorrhea produced no beneficial effects. The action of filtrates is that of an endotoxin.

I. DAVIDSOHN.

ACTIVE AND PASSIVE IMMUNIZATION AGAINST BACTERIOPHAGE. L. OELRICHS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:54, 1932.

Injections of dysentery bacteriophage in rabbits and mice produced immunity, evidenced by a rapid and thorough elimination of the bacteriophage when it was

subsequently injected. Serum of immunized rabbits passively immunized mice. Damage to the reticulo-endothelial apparatus only slightly influences active immunity.

I. DAVIDSOHN.

QUANTITATIVE CONDITIONS OF THE ANTIGEN-ANTIBODY REACTIONS OF LIPOIDS. A. J. WEIL, J. BERENDES and H. WEIL, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:69, 1932.

The actual quantities of the active principle of alcoholic organ extracts, of cholesterol and of lecithin which are needed for the stimulation of antibody production are much smaller than those commonly employed, and, when calculated as dry substance, can be expressed in milligrams. Still smaller are the quantities necessary for the reaction in vitro. Organ extracts are antigenically more efficient than synthetic lecithin and chemically pure sterols.

I. DAVIDSOHN.

ANTIGENIC QUALITIES OF CHOLESTEROL AND OF ITS DERIVATIVES. A. J. WEIL and F. BESSER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:76, 1932.

The various cholesterols differ in their antigenic qualities. Antibodies are produced against cholesterol, *di*-hydrocholesterol, oxycholesterol and viosterol when they are injected in a mixture with hog serum. The other members of the group are not able to stimulate production of specific antibodies in the animal. The comparison of the structural formulas shows that a very slight change causes the loss of antigenicity, e. g., the replacement of two atoms of hydrogen by bromine or oxygen.

I. DAVIDSOHN.

ISOLATION OF GROUP-SPECIFIC ANTIGENS OF HUMAN RED BLOOD CELLS. C. HALLAUER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:119, 1932.

The report is a continuation of a previous publication. It was necessitated by the fact that checks instituted by some investigators did not confirm the original report, while other workers, among them the abstractor, confirmed Hallauer's results. Hallauer arrived at the same results as previously: Agglutinogens A and B were partly separated by repeated washing with physiologic solution of sodium chloride in which they are present in soluble form. The diminution of the antigenic substance is sufficient to prevent an agglutination by a specific group serum, but the red cells were as able as nonwashed cells to absorb the agglutinins from the serum. The antigenic properties of the physiologic solution of sodium chloride used for washing the red cells were not due to the stroma of the broken-down cells, as was shown by means of various experiments.

I. DAVIDSOHN.

GROUP-SPECIFIC DIFFERENTIATION OF HUMAN ORGANS. L. A. SCHWARZMANN and N. N. JOUKOFF-WEREJNIKOFF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:134, 1932.

The method of Hallauer for the separation of the antigenic substances A and B from the red blood cells was applied to other organs (liver, brain, kidney and spleen), and it was shown that by repeated washings the substances A and B were separated from the tissues and taken up by the physiologic solution of sodium chloride. The absence of A and B after successful separation was demonstrated by the failure of the tissue to remove the agglutinins from a serum.

I. DAVIDSOHN.

BLOOD GROUP FERMENTS. ADOLPH STIMPFL, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:159, 1932.

The blood group ferments, which were discovered by Schiff and his associates, are substances able to destroy the agglutinogens A and B. They are found in

feces and in saliva. They are not due to the action of bacteria; they are filtrable and ferment-like. It could not be determined whether one or more ferments are present. Stimpfl studied the action of the ferment of the feces on the substances A and B present in the saliva, and on the A-like substance of the commercial Witte peptone. The efficiency of the ferment does not depend on the blood group of the person whose feces are the source. The ferment acts best between 27 and 47 C. A high temperature affects the destructive action of the ferment on the substance A to a more marked degree than it influences its action on substance B. The optimum p_H lies between 5.0 and 7.5. Mercuric chloride, mercurous nitrate and ferric chloride destroy the ferments even in high dilutions, while acetone is harmless even in 50 per cent dilutions. The effect of many other substances was studied. In its chemical qualities the ferment differs from the other ferments known to be present in the feces.

I. DAVIDSOHN.

SEROLOGIC ANALYSIS OF INTESTINAL MUCOSA. E. WITEBSKY and A. ZEISSIG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:266, 1932.

Rabbits were immunized with suspensions prepared from the mucosa of various portions of the intestinal tract of the ox. Besides nonspecific lipoid antibodies, which are sometimes formed, there is evident in some antiserums a strict organ specificity, to such an extent that antiserums produced by injections of certain anatomically different portions of the stomach or of the duodenum fixed complement only with alcoholic extracts of homologous organs and not with others. It was also observed that the specificity was strictly individual, so that a reaction took place with tissue extracts not of the same organs but of different individuals. The development of group-specific immune serums was observed, due to the presence of the antigen A in the ox, extracts of whose organs were injected into the rabbit. Immunization of rabbits with suspensions of the mucosa of the intestinal tract of hogs failed to produce lipoid antibodies. The development of species-specific antibodies was marked. After proper absorptions for the removal of the species-specific antibodies, organ specificity of the immune serums became apparent.

I. DAVIDSOHN.

EMPLOYMENT OF PALLIDA ANTIGENS FOR THE SERODIAGNOSIS OF SYPHILIS. R. R. HOELTZER and S. M. JUNUSSOWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:322, 1932.

The antigen consisted of washed spirochetes suspended in a mixture of two parts of physiologic solution of sodium chloride and one part of alcohol. It proved more satisfactory than the alcoholic pallida extracts and did not become anti-complementary, even after eight months at room temperature and two months in the incubator. It was more sensitive than the organ extracts, and when employed in the complement fixation test, it proved slightly superior to the Kahn test.

I. DAVIDSOHN.

EFFECT OF HUMAN BLOOD SERUM ON HUMAN TUBERCLE BACILLI. P. KALLÓS and E. NATHAN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **76**:343, 1932.

The synthetic culture medium of Kirchner with the addition of serums of patients suffering from cutaneous or pulmonary tuberculosis or of healthy persons was employed. Only the serum of patients with tuberculosis of the skin had an inhibiting effect on the growth of tubercle bacilli. Morphologic changes were also observed after cultivation for four weeks. This effect was not observed when the serum and the tubercle bacilli were from the same host.

I. DAVIDSOHN.

DISTRIBUTION OF AN ARSENIC CONTAINING ANTIGEN IN THE ORGANISM. FELIX HAUROWITZ and FRIEDRICH BREINL, Ztschr. f. physiol. Chem. **205**:259, 1932.

P-aminophenylarsenic acid was injected into rabbits. The larger part of the antigen injected disappeared in a few hours from the blood, and after twenty-four hours the arsenic content of the blood had returned to a normal level. The main quantity of the arsenic was retained in the liver and bone marrow (reticulo-endothelial system). The peak of the arsenic content of these organs was obtained six hours after injection. The arsenic content of the spleen was high, but as this organ is small in the rabbit, it did not play an important rôle in the binding of the arsenic. The arsenic content of the brain, skin and muscle was not appreciably increased. Somewhat higher values were found in the lung. A not inconsiderable fraction of the arsenic content of the liver and bone marrow must be referred to their blood content. The arsenic content of the kidney was very high, apparently owing to the presence of split products of the antigen to be excreted with the urine, which contained large amounts of arsenic. Two thirds of the antigen were excreted after eight days. While the arsenic found in the organs shortly after injection was apparently present in an unchanged form, the arsenic retained over ten days in the liver, bone marrow, etc., existed there in a changed and bound form of unknown character.

WILHELM C. HUEPER.

TUBERCULOUS IMMUNITY AND COMPLEMENT FIXATION. K. L. PESCH, Ztschr. f. Tuberk. **65**:121, 1932.

Normal rabbits occasionally show nonspecific complement fixation with tuberculous antigens. Complement-binding bodies can be produced by the injection of living or dead human tubercle bacilli and of B C G. It is further possible to produce complement-fixing bodies by intravenous injections of tuberculin or of water soluble albuminoid metabolic products of tubercle bacilli. Immunized rabbits survive normal controls for a considerable period following a virulent bovine infection. No relation exists between complement fixation and immunity. Immunity could not be produced with tuberculin.

MAX PINNER.

ASPECIFIC WASSERMANN REACTIONS. J. FORSSMAN, Acta Soc. med. fenn. duodecim **15**:1, 1932.

Forssman defines an aspecific Wassermann reaction as one occurring with serums of patients suffering from nonsyphilitic diseases. The difficulty in establishing a truly aspecific reaction is due to the fact that syphilitic persons are frequently free from clinically recognizable symptoms for a long period of time. The disappearance of the positive Wassermann reaction in the absence of specific antisyphilitic treatment may be regarded as proof that the reaction was nonspecific. This, however, should be taken more as a guiding rule than as a fixed law, since: (1) Truly positive reactions often disappear following malarial treatment (as in dementia paralytica) or following the onset of secondary nonsyphilitic infections; (2) positive Wassermann reactions in doubtful cases may become negative for only a time; (3) some months may pass before an aspecific reaction may disappear. In a series of examinations of 7,711 patients at the medical university clinic at Lund, Sweden, Forssman obtained positive Wassermann reactions with the serums of 203 patients. Ten of the 203 positive reactions were ascertained as aspecific. Five patients gave negative reactions on repeated examination. Of the remaining 5 patients, 3 had disease of the lung; all 5 (0.65 per cent of the total number) gave a negative reaction only after several months. Unless extreme diagnostic and serologic acumen is used there is a chance that such cases may be regarded as syphilitic. The following were the conditions in which aspecific Wassermann reactions were obtained: septicemia and pneumonia; bronchopneumonia; exudative pleurisy; pleurisy (sicca sanata); croupous pneumonia; septicemia; tuberculous (?) pneumonia; tertiary malaria; polyarthritis and pericarditis; lymphadenoma universalis. The tabulation of the results discloses the interesting and important fact that in each of the 10 cases presented the Kahn reaction ran parallel with the Wassermann reaction (cholesterolized antigen).

Tumors

INTRACELLULAR FAT IN MAMMARY TUMORS. K. ZANDER, Virchows Arch. f. Path. Anat. **283**:458, 1932.

Forty carcinomas and forty benign neoplastic, inflammatory and involutional conditions of the mammary gland were examined for the presence of fat within the cells. Sudan III was used, and unstained frozen sections were examined for doubly refractile lipoids. Fat droplets stained by sudan III were found within the epithelial cells in practically every instance. Doubly refractile lipoids were detected only four times. The fat is held to be the result of degeneration, and not of the specific activity of the cells.

O. T. SCHULTZ.

CYSTADENOMA OF LYMPHATIC TRUNK. M. H. CORTEN, Virchows Arch. f. path. Anat. **283**:653, 1932.

Corten describes some unusual conditions brought to light in the necropsy of a woman aged 68. Along the entire lymphatic trunk were found cystic structures. These were aggregated into tumor masses in the neck at the mouth of the duct, at the cisterna, and in the region of the left suprarenal gland. The cysts were lined by epithelium that varied in height from flat cuboid to high columnar. The latter formed papillary ingrowths into the lumens of some of the cysts. Although the term lymphangioma is used in the title of the article, the cysts appear to have been epithelial structures, and in the body of the paper Corten uses the word cystadenoma. The patient also had a carcinoma of the gallbladder. The tumor of the neck, however, had been present since birth. Corten discusses the various theories that might explain the origin of the cystic tumors. He thinks it most likely that epithelium reached the lymphatic trunk from some unknown source and in some unknown way early in development.

O. T. SCHULTZ.

FIBROSARCOMA IN A WILD RABBIT. I. SZABÓ and MARGRIT SZABÓ, Virchows Arch. f. path. Anat. **283**:661, 1932.

The tumor was the size of a man's fist and was attached to the lower third of the vertebral column.

O. T. SCHULTZ.

POLYPOID TUMORS OF THE LEFT AURICLE OF THE HEART. W. MÜLLER, Virchows Arch. f. path. Anat. **284**:105, 1932.

Polypoid tumors of the left auricle have been frequently described, usually as myxomas. Prevailing opinion denies the blastomatous character of these structures and considers them to be organized thrombi. They should therefore be called pseudomyxomas. Müller describes four examples that had the gross characteristics of the so-called pedunculated myxoma, or pseudomyxoma. They were wholly different from each other in their histologic characters. All were of unusual size. The first was a finely fibrillated sarcoma. One portion extended into the right pulmonary vein and was directly continuous with a sharply circumscribed tumor nodule the size of a goose egg in the middle lobe of the right lung. In the left lung were three widely separated similar nodules. All of the nodules were composed of tissue identical with that of the growth in the heart. The second tumor was histologically more like what has usually been described as a myxoma. It was more highly vascularized, revealed no transitions from thrombus to tissue, and, Müller believes, the tissue, at the time of death, was that of tumor. He does not deny the possibility that an organized thrombus may have been transformed into a benign connective tissue tumor. Similarly for the first tumor, which was unquestionably malignant at the time of death, he does not deny the possibility of the transformation of the tissue of an organized thrombus into tumor tissue. In neither of the two cases, however, was there histologic evidence that the tumor had originated as a thrombus. The third polypoid tumor was histologically a thrombus in which no organization was evident. The fourth tumor was a broad-based mass

that arose from the interauricular septum and grew into and almost filled the auricular cavity. It was a spindle cell sarcoma, which Müller derives from a rhabdomyoma. There were multiple metastases in the lungs and other organs. In spite of the large size of the structures described, there were few cardiac symptoms during life.

O. T. SCHULTZ.

THREE MEDIASTINAL TUMORS OF THYMIC ORIGIN. H. HAMDI and HALIS, Virchows Arch. f. path. Anat. **284**:230, 1932.

Hamdi and Halis conclude that the thymic cells that gave rise to the tumors were epithelial in origin. The tumors occurred in men aged, respectively, 45, 61 and 53 years.

O. T. SCHULTZ.

TUMORS OF THE OVARY WITH TISSUE LIKE THAT OF THE THYROID GLAND. H.-A. HEINSEN, Virchows Arch. f. path. Anat. **284**:234, 1932.

Most of the authors whose work is reviewed by Heinsen hold that the tissue like that of the thyroid gland occasionally found in tumors of the ovary is true thyroid gland tissue. Most often such tissue is part of a dermoid or teratoma, and the presence of iodine in it is accepted as proof that the tissue is identical with that of the thyroid gland. Some authors, on the basis of colloid tumors of the ovary that did not contain teratoid tissue, have concluded that such tissue is never true thyroid gland tissue. The tumor described by Heinsen occurred in a woman aged 74. It was solid, but contained cystic spaces and tissue of the consistency of cartilage and bone. The author nowhere terms the tumor a dermoid or a teratoma. Histologically, the structure was that of a colloid struma of the thyroid gland. The tissue did not contain iodine. Some of the cystic spaces were filled with mucoid material that had the staining reaction of mucin. Some follicles were filled with colloid that had the staining reaction which Kraus considers specific for thyroid gland colloid. Although some tumors of the ovary may contain true thyroid gland tissue, as may be determined by the presence of iodine, other tumors of similar histologic appearance do not contain such tissue. Some of these are pseudomucinous cystadenomas; others are cystadenomas that have undergone colloid transformation. It is in the latter group that Heinsen places his tumor, and he proposes for this group the name cystoma colloides strumiforme.

O. T. SCHULTZ.

IMPLANTATION AND CONTACT METASTASES OF MALIGNANT TUMORS. R. BORRMANN, Virchows Arch. f. path. Anat. **284**:621, 1932.

Borrmann reports a case of implantation metastasis from a melanoma of the scalp on the endocardium of the auricular appendage of the right auricle, and one of contact metastasis of the pleura from a secondary carcinoma of the apposed interlobar pleura. Such metastases can occur only in surgical wounds, puncture canals and on serous membranes. They cannot occur on the outer skin or on the mucosa of the gastro-intestinal tract.

O. T. SCHULTZ.

PRIMARY CARCINOMA OF THE PERICARDIUM. O. SATKE and G. SALZER, Virchows Arch. f. path. Anat. **284**:632, 1932.

The authors report, as a primary carcinoma of the pericardium, a tumor that they derive from the surface cells of the pericardium. The illness, in a patient 56 years old, had begun three years prior to death with fever, and was followed by symptoms that led to a clinical diagnosis of chronic obliterative pericarditis. The latter condition was found at necropsy, and the authors believe that the tumor developed from the glandlike structures that are not infrequently seen in chronic adhesive pericarditis and that are derived from the surface cells. The reasons for preferring the term carcinoma to that of endothelioma or that of coelothelioma are briefly stated. Mesothelioma, as a possible preferable term, is not mentioned.

O. T. SCHULTZ.

MULTIPLE NEUROFIBROMAS: CASE WITH FIVE DIFFERENT TYPES OF TUMORS. O. FOERSTER and O. GAGEL, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:339, 1932.

Five different types of tumors were found in the brain of a 21 year old woman who had had numerous neurofibromas of various parts of her body since childhood. Some of these had been removed surgically, and some in the pelvis apparently gave rise to symptoms of salpingitis. For three years before death this woman had disturbances of hearing and for one year headaches, vomiting, double vision and a staggering gait. The blastomatous polymorphism of von Recklinghausen's disease is illustrated by the different types of tumors found in the brain. There were neurinomas of both acoustic nerves, of the left oculomotor nerve and of the first cervical root, a central neurinoma of the medulla oblongata, heaped-up glia elements scattered all over the brain, an angiomatous new growth and multiple meningiomas.

GEORGE RUKSTINAT.

COMPLEMENT-FIXING ANTIBODIES IN CARCINOMATOUS RABBITS. A. COHN and W. A. COLLIER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:174, 1932.

The rabbits suffered from a metastasizing carcinoma of the testicle. The antigen was prepared from tumor material. No complement-fixing antibodies could be detected. In rabbits given injections of the tumor material, very faint complement fixation was observed; it was more pronounced, though only transient, when the lipoids of the cancerous tissue combined with hog serum were injected into the animals. The cancer antigen could be used for the performance of the Wassermann reaction with the rabbit serum.

I. DAVIDSOHN.

COMPLEMENT FIXATION IN CARCINOMA. OLOF SIEVERS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **74**:257, 1932.

By employing the technic and alcoholic cancer antigen of Hirszfeld and Halber, the results obtained with serums in 229 cases were similar to those of the last mentioned authors. Also the results obtained with the cholesterol antigen were comparable to, though considerably lower than, those of Eisler and Jacobsohn. Complement fixation occurred with serums of rabbits not previously treated with cancerous organs. Most of these rabbits were pregnant, and the reaction turned negative after puerperium; still there remained some normal nonpregnant rabbits giving constantly a positive complement fixation. This throws a new light on the claim of Hirszfeld and Halber of having produced specific anticancerous immune serums in rabbits by treating them with cancerous tissue.

I. DAVIDSOHN.

Medicolegal Pathology

PSYCHOPATHOLOGIC SYMPTOMS IN LEAD POISONING. H. A. SCHMITZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:391, 1932.

Since lead selectively attacks the nervous tissues, psychic disturbances are commonly observed in lead poisoning. Development of neurasthenic complaints in a lead worker, who previously did not exhibit any neuropathic or psychopathic symptoms, should caution one to consider seriously an organic lead injury of the central nervous system. The same is true of the occurrence of a premature cerebral arteriosclerosis in comparatively young workers who are constantly employed in lead industry. After exposure to lead for from fifteen to twenty years, arteriosclerosis is commonly found. The faculties of attention, concentration and memory are disturbed, often to a noticeable degree. Rawkin found a lack of memory in 80 per cent of his patients with lead poisoning. A clinical diagnosis of lead psychosis cannot be made from the psychopathologic symptoms alone, but must be based on other positive signs of lead poisoning.

E. L. MILOSLAVICH.

DEATH FROM STEAM INHALATION. G. GUARESCHI, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:409, 1932.

Since the literature does not give any exact information as to the cause of death by inhalation of steam, experiments were made on rabbits which disclosed that exposure to steam escaping under pressure of 1 and 2 atmospheres caused the respirations to cease rapidly and completely after a few deep inspirations. Death is caused by paralysis of the respiratory musculature. When the steam was released freely, without pressure, however, one noticed first a dyspneic period of inspiratory type, then complete apnea, followed by a dyspneic phase of expiratory character. Death occurs by asphyxiation. As to the mechanism of death, one has to consider not only the injurious effect on the bronchial mucous membrane of the temperature of the steam being inhaled, but also the rapidly developing mucous hypersecretion due to irritation by the steam and the respiratory embarrassment resulting therefrom.

E. L. MILOSLAVICH.

DEATH FROM SHOCK DURING BOXING MATCH. P. TYRELL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:415, 1932.

A 34 year old man suddenly collapsed after a blow to the chest during a boxing match and died within a few minutes. Except for a large thymus, the observations at autopsy were insignificant. Death was attributed to shock. Boxers' deaths can be classified into two groups, those caused by injuries to the vital organs and those resulting from shock.

E. L. MILOSLAVICH.

TRAUMATIC ANEURYSMS OF THE BASAL CEREBRAL ARTERIES. F. HARBITZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:463, 1932.

Aneurysms of the basal arteries of the brain are comparatively common and usually lead to intermeningeal hemorrhages of lethal character. They occur spontaneously on account of atherosclerotic changes and may produce various clinical symptoms, such as intermittent apoplectic insults. Some are unquestionably caused by severe injuries to the head, particularly those found in young persons in whom atherosclerotic factors can be eliminated. Certain developmental anomalies may play an important rôle in their formation. The traumatic origin of some aneurysms is further proved by the occasional finding of healed intramural tears and by the occurrence of total lacerations of otherwise normal-appearing arteries following severe cranial injuries.

E. L. MILOSLAVICH.

PATHOLOGIC ANATOMY OF ACUTE FLUORIDE POISONING. N. GELLERSTEDT, Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**:475, 1932.

A 49 year old man ingested, with suicidal intent, about 1 Gm. of sodium fluosilicate and died three and one-half hours afterward. The clinical picture was characterized by severe abdominal pains and cramps, vomiting, diarrhea, convulsions and coma. The autopsy showed a pronounced venous congestion and marked hemorrhages of the mucous membrane of the stomach and duodenum. The microscopic examinations disclosed an acute superficial gastritis, with hyperemia, hemorrhagic infiltration and edema of the mucosal tissues. There was a fatty degeneration of the heart muscle, of the central zones of the hepatic acini, and of the convoluted tubules of the kidneys, with hemolysis of the erythrocytes.

E. L. MILOSLAVICH.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, Jan. 12, 1933

MORTON MCCUTCHEON, *Vice-President, in the Chair*

INCIDENCE AND SEVERITY OF ARTERIOSCLEROSIS IN FIVE HUNDRED AUTOPSIES. WILLIAM B. WARTMAN.

An analysis was made of 500 unselected cases in which autopsy was performed in order to determine the incidence, distribution and degree of arteriosclerosis in the various organs of the body. The postmortem records were examined for mention of gross arteriosclerosis and the sections for microscopic evidences.

The percentage of incidence of gross arteriosclerosis in the various organs was as follows: brain, 80; aorta, 74; heart, 57, and kidney, 56. These four organs only are mentioned, as sufficient data concerning the others were not available.

The percentage of incidence of arteriosclerosis in the various organs as determined by histologic examination of the sections was: spleen, 89; aorta, 88; brain, 82; kidney, 73; suprarenals, 61; pancreas, 57; heart, 53; gastro-intestinal tract, 42; lung, 34; liver, 28, and diaphragm, 6. When the organs were arranged in order of decreasing incidence of arteriosclerosis, it became apparent that those which were most often involved were also most markedly affected by an arteriosclerotic process. Thus the arteries of the spleen, aorta, brain and kidney were sclerosed to a marked degree in 70 per cent of the cases involving these organs, while those of the liver, lungs and gastro-intestinal tract showed marked sclerosis in less than one third of the cases, and those in the diaphragm did not show marked arteriosclerosis in any case.

Among the 500 patients there were 303 males and 197 females. The youngest was an infant born prematurely at the sixth month, and the oldest, a man aged 92. In order to condense the data, the patients were divided into three age groups; under 29 years, from 30 to 59 years and from 60 to 92 years. Analysis indicated that the incidence and degree of arteriosclerosis increased with age. In the spleen and kidney, for example, there was a high incidence of arteriosclerosis with a correspondingly low incidence of normal vessels. This relation gradually became more apparent as the ages of the patients advanced, until finally, in the group between 60 and 92 years, more than two thirds exhibited marked sclerosis. The reverse was found in the diaphragm, where the great majority of the arteries were free from sclerosis even in the advanced age group.

The most striking feature was the great infrequency of sclerosis of the diaphragmatic arteries and arterioles. The relative infrequency of sclerosis in the arteries of the voluntary muscles is substantiated by the results of all workers with the exception of Kernohan and his collaborators. The results indicate also that a generalized arteriosclerotic process sufficiently advanced to be of clinical significance occurs infrequently.

UNUSUAL CORONARY LESIONS. HERBERT LUND.

To ascertain causes of coronary occlusion other than arteriosclerosis, a survey was made of the records of 2,100 necropsies at the Philadelphia General Hospital. The causes found are as follows:

Syphilis.—Syphilis is supposed to be an important cause, yet only one case was found in which syphilitic aortitis was directly responsible for death from coronary occlusion. In this case the coronary orifices were so small that the point of a probe could not be introduced.

Including the case just mentioned, there were eight cases of syphilitic stenosis of the coronary orifices. The findings are tabulated as follows:

Stenosis of both orifices	5
Stenosis of right orifice	2
Stenosis of left orifice	1
Associated aortic regurgitation	3
Associated with no cardiac symptoms (Right orifice; no aortic regurgitation)	1
Longest duration of symptoms (Both orifices; no aortic regurgitation)	3 years
Duration of symptoms, excluding the foregoing two cases	10 weeks to 1 year
Largest heart (Aortic regurgitation and stenosis of both coronary orifices)	820 Gm.
Average weight of remaining seven hearts (300 to 460 Gm.)	390 Gm.
Race: Negro	8
White	0
Age	40 to 54

In most cases the duration of cardiac symptoms was comparatively brief, and there was no great hypertrophy of the heart.

There were four cases of syphilitic aortitis with a coincident myocardial infarction from some other cause.

Generalized Endarteritis Obliterans.—A Negro, 30 years of age, who had complained of transient blindness and shortness of breath, died of peritonitis caused by a perforated jejunal ulcer. The heart showed a recent infarction of the left ventricle which was bulging out as an aneurysm. Microscopically, the vessels of the viscera presented marked proliferation of the intima and media with narrowed lumen and frequent arteriolar occlusions. The round cell collar and the leukocytic infiltration of the vascular walls gave evidence of the inflammatory nature of the process. It was thought that the vascular lesion was responsible for the jejunal ulcer.

Periarteritis Nodosa.—An Italian of middle age, who complained of "stomach ache" and inability to walk, died four weeks after the onset of symptoms. Clinically, he had hypertension, retinal hemorrhages and choked disks and a leukocyte count of 22,000. At necropsy, nodules were found on the blood vessels of the thoracic and abdominal viscera, notably on those of the heart, liver, pancreas and gallbladder. There was a thrombotic lesion in the brain. At intervals along the coronary arteries, small aneurysm-like bulgings occurred. These contained slow, cumulative thrombi. Apparently, sufficient anastomosis was established during the occluding process that frank myocardial infarction did not occur.

Rheumatic Fever.—Rheumatic fever is a carditis attended by typical coronary lesions, which have been described by Pappenheimer and Von Glahn. One case was found in which there were marked arterial changes. The arterial walls were thickened and infiltrated by a pink-staining collagenous mat. About them was a loose fibrillar stroma containing the usual mixture of Aschoff cells, lymphocytes and eosinophils. Many arterioles were completely occluded. The myocardium presented marked degeneration which in places had almost the appearance of infarction.

Thrombosis of Unknown Etiology.—In one case there was a thrombus in the left anterior descending artery with a recent myocardial infarction and mural thrombus. There was no arteriosclerosis (the patient was only 23 years of age), nor was syphilis or any source of embolism demonstrable. A second case, similar to this, was not considered, because the description was incomplete.

Embolism.—Three instances of myocardial abscess were recorded. One of these was a result of pyemia; in the other two cases there was a coincident endocarditis.

Frank infarction due to embolism was not as frequent as was expected. One case was found which may have had an embolic origin. The patient had subacute endocarditis and died suddenly. At necropsy, brittle vegetations were found on

the aortic leaflets, and there was an area of softening in the left ventricle. Coronary sclerosis with moderate myocardial fibrosis was present as well, which cast doubt on the likelihood of an embolic phenomenon. Textbooks on pathology often stress embolism as much as arteriosclerosis as a cause of infarction. This does not seem justified.

Thrombosis of the Coronary Veins.—An organized, recent thrombus was found in an arteriosclerotic heart. Its significance is probably trivial.

In the series of 2,100 necropsies, 80 cases of myocardial infarction were found. All of these, with the exceptions noted, were due to arteriosclerosis. Syphilis and embolism are apparently given more importance than they deserve.

THE GENESIS OF SHOCK IN MERCURIC CHLORIDE POISONING. V. H. MOON and B. L. CRAWFORD.

This paper was published in full in the ARCHIVES OF PATHOLOGY (**15**:509, 1933).

Regular Meeting, Feb. 9, 1933

V. H. MOON, *President, in the Chair*

The William Wood Gerhard gold medal of the Pathological Society of Philadelphia was presented to Dr. Frank C. Mann, of the Mayo Foundation, Rochester, Minn. Following this, Dr. Mann gave the annual conversational lecture, his subject being "Observation on Experimental Pathology and Pathologic Physiology of the Liver."

Regular Meeting, March 9, 1933

V. H. MOON, *President, in the Chair*

This meeting was devoted to a program in commemoration of the seventy-fifth anniversary of the society.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, Jan. 9, 1933

PAUL R. CANNON, *President, in the Chair*

PATHOGENESIS OF EXPERIMENTAL PNEUMOCOCCIC LOBAR PNEUMONIA IN THE DOG. O. H. ROBERTSON, L. T. COGGESHALL and EDWARD E. TERRELL.

Experimental lobar pneumonia was induced in dogs by the injection into a terminal bronchus of pneumococci suspended in a viscous starch broth medium. This disease resembled lobar pneumonia as seen in human beings in many respects, both in its clinical course and in the pulmonary pathologic process. In order to study the evolution of the experimental lesion, animals were killed from one to twenty-four hours following the initiation of the infection. Within one hour after the implantation of pneumococci, suspended in a starch broth medium, into a terminal bronchus, a definite local inflammatory reaction occurred. This consisted of a central cellular infiltration, hemorrhagic and exudative, surrounded by alveoli filled with edema fluid in some parts, and with starch in others, and accompanied by engorgement of the blood vessels, the larger of which showed perivascular edema. The lesion showed progressive growth, extending radially from the initial focus. This process was characterized by an advancing zone of edema-filled alveoli

which in turn were gradually invaded by polymorphonuclear leukocytes and red blood cells until they were filled and distended by the exuded cells. Inflammation of the interalveolar septums was an inconspicuous feature, although peribronchial and perivascular edema was marked. The pathologic lesion at first was definitely lobular or circumbronchial, but after a few hours lost its association with bronchi and became a continuous area consisting principally of intra-alveolar cellular exudate. By the end of from six to twelve hours the oldest portion of the lesion began to suggest the mosaic appearance of the human lung in lobar pneumonia. Within twenty-four hours, usually, a whole lobe was consolidated, and at times extensions to other lobes occurred.

Dispersion of the pneumococci within the first few hours appeared to take place principally through the pulmonary parenchyma, since they were observed in considerable numbers in the walls of alveoli which appeared normal and lay beyond the margin of the zone of edema. Later the character of the distribution suggested that the pneumococci were also carried by the edema fluid through the smaller air passages. Marked regional differences in the distribution of the micro-organisms were observed. At the periphery of the lesion they were present in great numbers, lying free in the edema-filled alveoli. In the immediate underlying zone of cellular exudate they were fewer and lay partly within the polymorphonuclear leukocytes, while in the oldest part of the lesion, showing intense cellular infiltration, relatively few were seen, and these were practically entirely intracellular. On the basis of these observations certain inferences were drawn concerning the propagation of pneumococcic infection in the lung of the dog.

DISCUSSION

EDWIN F. HIRSCH: Did the virulence of the strain of pneumococci have any bearing on the production of the lobar pneumonia? If the virulence is not the only factor concerned in the experimental production of lobar pneumonia in dogs, what mechanical action has the starch solution used as a conveying medium?

PAUL R. CANNON: Was there evidence that fibrin acted as a localizing agent, and were cultures of the blood made?

O. H. ROBERTSON: Starch solution has a definite localizing effect and was found effective after many other mediums had failed. Strains of pneumococci with low virulence for mice are not effective in dogs; consequently strains of high virulence were necessary. Fibrin is always seen in the initial stages of the lesions. Bacteria were cultured from the blood during the first stages of the disease, but not later. In this respect the disease in dogs resembles human infections.

NASOPHARYNGEAL CARCINOMA. OSCAR CHRISTIANSON and S. W. MCARTHUR.

Three primary nasopharyngeal carcinomas with bilateral metastases to the cervical lymph nodes were described grossly and histologically. The diagnosis in each case was made clinically by examination of surgically excised tissues. One patient was examined post mortem. Histologically all the tumors consisted of small epithelial cells laid down in mosaics, and they resembled immature squamous or pseudostratified epithelium. Slight variations in cellular structure occurred in these carcinomas, but within the limits of the varieties of cells in the pseudostratified epithelium lining the nasopharynx.

An essential clinical feature of these tumors was the insidious and painless bilateral enlargement of the cervical lymph nodes due to metastases. The bilateral distribution of the metastases resulted from the midline location of the primary growth, and from the dissemination of the tumor tissue into the lymphatics on both sides of the neck.

The complete report will be published in the *Archives of Surgery*.

IMPLANTATION AND STRUCTURE OF A HUMAN OVUM NEAR THE SEVENTEENTH DAY (PRIMITIVE STREAK STAGE). JOHN I. BREWER and H. O. JONES.

The human ovum reported was normal and anatomically complete. An accurate history of coitus and of menstrual periods was obtained from both husband

and wife. The external measurements of the chorionic vesicle in the fresh state were 8 by 7 by 4 mm., and the internal measurements were 6 by 5 by 2.5 mm. The yolk sac was 1 mm. in diameter before fixation. The amniotic cavity after fixation was 0.816 by 0.66 by 0.2 mm. The embryonic plate in the prepared slide was 0.65 by 0.78 mm. The longest villus was 0.1 mm. Blood vessels were differentiated in the villi, the body stalk and the yolk sac. The development of the vessels was in situ. The cytotrophoblast originated in the villi and spread over the surrounding decidua. Formation of syncytium was traced from these cells. The cytotrophoblastic cells contained glycogen, and some contained lipoid droplets. The syncytium had no glycogen, but in many of the masses there were lipoid droplets. Differentiation of fetal and maternal cells could be made with the aid of glycogen and mitochondrial stains and by the cell forms.

The embryonic plate had a short primitive streak. There was no neurenteric canal. A definite cloacal membrane was present, and an allantoic diverticulum 0.29 mm. in length extended into the body stalk.

ANGIOMATOUS MALFORMATIONS OF THE BRAIN. REPORT OF TWO CASES OF ANGIOMA RACEMOSUM. VICTOR LEVINE.

The complete report will be published in the ARCHIVES OF PATHOLOGY.

PAUL R. CANNON, *President, in the Chair*

Regular Meeting, Feb. 13, 1933

TRAUMATIC SHOCK SYNDROME FOLLOWING RUPTURE OF THE AORTA AND MULTIPLE FRACTURES. NORMAN W. ROOME.

A case of traumatic rupture of the aorta, possibly due to indirect violence, was reported. In addition there were multiple fractures of the ribs, sternum, pelvis and left leg. It was estimated that over 1,200 cc. of blood had been lost from the circulation; there was also moderate pulmonary fat embolism

The traumatic shock syndrome was exhibited, and the patient died eight hours after admission to the hospital. There was thought to be an adequate anatomic basis for the depression of the circulation (i. e., by local loss of fluid, as found experimentally by Blalock, Phemister and others, with pulmonary embolism and mediastinal tamponade), without assuming the liberation of a histamine-like toxin from the damaged tissues, as suggested by Cannon and others.

DISCUSSION

R. H. JAFFÉ: Traumatic rupture of the aorta, 3 or 4 cm. above the aortic ring and at the attachment of the ductus botalli, is regularly seen in aviators whose death is caused by falling from a high altitude.

H. ENZER: In the body of a man who collapsed after having been struck on the sternum by a golf ball, but who recovered and then died suddenly a week later, I found that death was due to laceration of a syphilitic aorta with hemopericardium.

D. B. PHEMISTER: The clinical problem in this patient was an explanation for the fall in blood pressure.

CONGENITAL VALVES OF THE POSTERIOR URETHRA IN TWINS. I. DAVIDSON and CHARLES NEWBERGER.

This report will be published in full in a later issue of the ARCHIVES.

EXPERIMENTAL BONE SARCOMA. ALEXANDER BRUNSCHWIG and PAUL H. HARMON.

When small fragments of a transplantable rat spindle and polyhedral cell sarcoma (rat tumor no. 256) are implanted into the marrow cavity of the femur or tibia of young rats, the following changes take place: The tumor grows to fill the marrow cavity, stopping at the epiphyseal lines. It grows outward through the haversian canals of the cortex, causing some absorption of bone, raises the periosteum for some distance from the surface of the cortex and grows through the elevated periosteum to compress and finally to infiltrate the muscles of the extremity. In the zone between the elevated periosteum and surface of the cortex there are trabeculae of bone, radiating at right angles to the surface of the shaft. Between these trabeculae are tumor cells, and it is difficult from morphologic study alone to be sure that these tumor cells are not being incorporated into the bony trabeculae as bone cells. This newly formed bone, which serves as a supporting framework for the tumor, is in reality of periosteal origin and has been formed by the periosteum as it was slowly elevated by the growing tumor.

When small fragments of this newly formed bone with adherent sarcoma cells are transplanted to the subcutaneous tissues of other rats the bone trabeculae die, but the sarcoma cells proliferate to form a simple spindle and round cell sarcoma about the dead bone. This demonstrates that no tumor cells have become osteoblastic, for if they had, new bone would have been produced in the transplant.

When a segment of femur with attached periosteum is obtained from a young animal, the contents of the medullary cavity are removed, a small fragment of tumor replaced in the marrow cavity and the whole implanted into the subcutaneous tissues of another animal, the tumor will grow through the cortex and elevate the periosteum, causing it to form bony trabeculae at right angles to the surface of the bony transplant. Beyond the raised periosteum the tumor grows as a fibrosarcoma without ossification.

The gross and histologic structure of the tumor resulting when the sarcoma is implanted into the medullary cavity or beneath the periosteum is practically identical with those bone sarcomas seen in man and commonly referred to as sclerosing osteogenic sarcomas. The conclusion to be drawn from these experiments, therefore, is that sclerosing osteogenic sarcoma is essentially a fibrosarcoma arising in the medullary cavity or subperiosteally; that in growing, it elevates the periosteum, permitting this to form bone, and that the bone is not all the result of metaplasia of tumor cells into osteoblasts, as is usually maintained in this type of bone neoplasm.

DISCUSSION

R. H. JAFFÉ: It is difficult to decide from a small piece of tissue that a bone growth is osteogenic. Only a few metastases of bone sarcomas produce bone.

PAUL R. CANNON: Are there any primary bone sarcomas in rats?

A. BRUNSCHWIG: Some bone sarcomas have been studied in lower animals, but little comment has been made about the metastases. In Miss Slye's mouse material there is a primary bone tumor, and the metastases in the liver have the same structure.

TUMORS OF THE SUPRARENAL CORTEX WITH REPORTS OF THREE CASES OF CARCINOMA AND A LIPOMA. FORD K. HICK.

Adenomas of the cortex of the suprarenal gland are incidental observations of unknown significance, possibly an index of previous phases of activity and inactivity of the gland. Sexual alterations, usually masculation in female, accompany hyperplasia or tumors of the cortex, and may be absent in anaplastic growths. Malignant tumors invade the veins and spread metastases to the liver and lungs. Carcinomas of the suprarenal cortex differ from the Grawitz tumors of the kidney, and should not be designated as hypernephromas. A woman, aged 35, had a carcinoma of

the cortex of the left suprarenal gland, carcinomatous invasion of the inferior vena cava and extensive metastases. There were also a primary carcinoma of the transverse colon and secondary growths in the liver and mesentery. Another patient, a man aged 31, had a carcinoma of the cortex of the right suprarenal gland with involvement of the kidney and metastases to the periaortic lymph nodes, liver, lungs and right kidney. A third patient, a woman aged 38, had an egg-sized carcinoma of the cortex of the left suprarenal gland. Death was caused by other disorders. A man, aged 50, died of a hypernephroid carcinoma of the kidney with extensive metastases. In the cortex of the left suprarenal gland there was an encapsulated nodule, 17 mm. in diameter, composed of differentiated fat cells.

Book Reviews

Intracranial Tumors. By Percival Bailey, Professor of Surgery, University of Chicago. Price, $6. Pp. 475, with 155 illustrations. Springfield, Ill.: Charles C. Thomas, 1933.

Following three chapters of an introductory and general nature, the various forms of intracranial tumors are considered in detail with particular reference to their structural characteristics. There are sections on acoustic neurinoma, hypophyseal adenoma, craniopharyngioma, tumors of the intracranial connective tissue (sarcoma, melanoma), meningioma, tumors of the vascular system (hemangioblastoma, certain malformations), and on the encephalic tumors proper: glioblastoma multiforme, astrocytoma, medulloblastoma (the old sarcomatosis of the pia), oligodendroglioma, spongioblastoma, astroblastoma, ependymoma, pinealoma, ganglioneuroma and neuro-epithelioma. In this grouping of encephalic tumors, the author follows in the main the classification in his "Histologic Atlas of Gliomas" (ARCH. PATH. **4**:872, 1928).

The glial tumors are grouped according to the predominating cellular type, descriptions of which are beginning to make their way into textbooks. The morphologic and biologic characteristics of each group of tumor, on the increase in knowledge of which depend progress in diagnosis and treatment, are set forth clearly on the basis of first-hand observation and independent study. Even each type of glioma is a distinct entity. The concluding chapters deal with metastatic intracranial tumors and with the problems of treatment.

The presentation is direct, fluent and straightforward, without the customary citation of authors. There is a good bibliography at the end. The book is printed on dull paper so that the reader can avoid "being blinded by the usual glossy paper used for medical books." On account of the dull paper pen-and-ink drawings are used, with excellent effect. One wishes that the method of preparation and staining had been given in connection with the drawings of the microscopic sections. The publisher's part is well done. The book is designed primarily for students and is in fact an amplification of a series of demonstrations and clinics for teaching purposes. The book is of interest to the pathologist because it describes thoroughly and competently in the light of the recent advances in knowledge the various intracranial tumors, and that is the reason for this brief review. The development in the surgical treatment of intracranial tumors is associated with an intensive study of the structure and varieties of such tumors by certain surgeons. The work of Harvey Cushing, whose pupil and former associate is the author of the book now under consideration, immediately comes to mind. In fact, the recent advances in this field are the result largely of investigations with newer technical methods by surgeons who realize that progress in diagnosis and treatment depend on the understanding of the characteristics of each type of tumor. To this work the author is an important contributor.

Practical Hematological Diagnosis. By O. H. Perry Pepper, M.D., Professor of Clinical Medicine, University of Pennsylvania; Assistant Chief of the Medical Clinic, Hospital of the University of Pennsylvania, and David L. Farley, M.D., Physician to the Pennsylvania Hospital, Philadelphia; Physician to the Cooper Hospital, Camden, N. J.; Associate in Medicine, University of Pennsylvania. Cloth. Price, $6, net. Pp. 562, with 3 colored plates. Philadelphia: W. B. Saunders Company, 1933.

This book aims to present the essentials of clinical hematology with as few confusing complications in nomenclature and method as possible. It uses simple terms and an arbitrary selection of methods. The chemical, bacteriologic and

special immunologic aspects of the blood are not included, as will be seen from the following outline of the contents.

The book is divided into three parts. The first part deals with the components of the blood, the methods of their study and the significance of the results thus obtained. The origin and development of the blood cells, the red cells, hemoglobin, the white cells, the platelets, coagulation, the blood groups, the hematologic side of transfusion and the parasites of the blood are presented in this part. The second part takes up the hematologic diagnosis of the diseases of the hematopoietic system. The hematology of the anemias, of polycythemia, of the leukemias, of the purpuric and hemorrhagic diseases, of infancy, of irradiation, of splenectomy, of lead poisoning and of other forms of poisoning is described in detail. The third part describes briefly the blood pictures in a large variety of diseases that are not primary diseases of the blood.

Three original, well executed colored plates show various forms of red and colorless blood cells as seen with Wright's stain. A list of hematologic terms not used in the text, with definitions, is appended. There are frequent references to the important recent literature. The style is clear and direct. The book will be a serviceable, helpful and reliable guide in practical hematology.

CORRECTION

In the article by Dr. Charles W. McLaughlin and Dr. James S. P. Beck, entitled, "Multilocular Cystic Lymphangioma of the Spleen," which appeared in the May issue (ARCH. PATH. **15**:655, 1933), the following statements should be substituted for those beginning with the twelfth line on page 662 and extending to the end of the paragraph.

A fluid pressure of 1 cm. of water per square millimeter in an afferent channel is transmitted as 1 cm. of pressure per square millimeter of surface in the cyst. It is possible, under suitable conditions, for a large cyst to have an increased hydrostatic pressure due to the weight of the fluid. Bernoulli's theorem is applicable when the velocity of the fluid in the afferent channel is high and when the widening in the channel is appreciable, but in physiologic conditions this would probably be negligible.

Obituary

WILLIAM OPHÜLS

1871–1933

William Ophüls died April 27, 1933, after a lingering illness. His loss is mourned not only by his associates and students in Stanford University Medical School, in which he was pathologist, teacher, dean, but also by the medical profession of the entire Pacific Coast. His was here the last word on pathologic problems and histologic diagnosis.

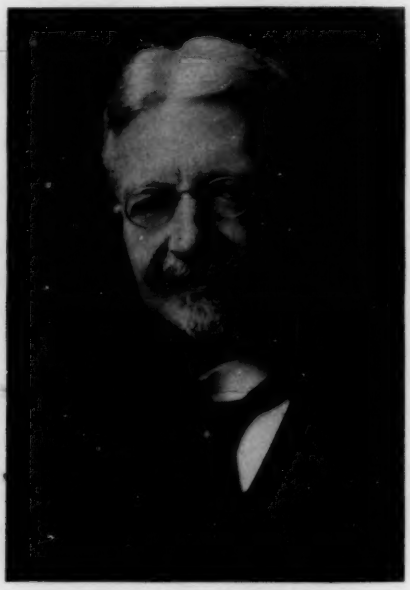
Born in Brooklyn, Oct. 23, 1871, eldest son of Carl and Clara Ophüls (née Wilhelms), William Ophüls was taken to Germany in his early childhood. He attended high school (Gymnasium) in Crefeld, and the University of Würzburg from 1890 to 1893, where he was a member of the student corps, Rhenania. The year 1894 was spent in the University of Berlin, and in 1895 the degree of doctor of medicine was received in Göttingen. For two years, 1896 and 1897, he was assistant in the pathologic institute of the University of Göttingen under Prof. Johannes Orth. On coming to America, Dr. Ophüls was almost immediately appointed professor of pathology and bacteriology in the University of Missouri at Columbia, where he spent one year, parts of 1897 and 1898. On the recommendation of Dr. William H. Welch, Dr. Ophüls was called to the chair of pathology in Cooper Medical College in San Francisco, which position he held until 1912 when Cooper College graduated its last class. In 1909, when Stanford University organized its medical department, Dr. Ophüls was appointed professor of pathology. He served as secretary of the faculty for a time until 1916, when Dr. Ray Lyman Wilbur, dean, was made president of the university. Dr. Ophüls succeeded him in the office of dean, which position, as well as that of professor of pathology, he filled until 1932, when he was obliged by illness to cease active work.

Dr. Ophüls occupied a number of other important positions; e. g., he was president of the San Francisco Board of Health from 1906 to 1909, and a fellow of the Rockefeller Institute from 1905 to 1908. He was a member of a number of important societies, such as the American Association of Pathologists and Bacteriologists, American Medical Association, California State Medical Society, California Academy of Medicine, Society for Experimental Biology and Medicine and San Francisco Pathological Society, and was a member of the editorial board of the ARCHIVES OF PATHOLOGY from its inception. He was a

member of Alpha Omega Alpha, Nu Sigma Nu and Sigma Xi and also of the University and the Commonwealth Clubs of San Francisco.

On May 6, 1903, he married Emmy Feldman of New York. They had four children, Clara, Ernst, Elinor (now Mrs. W. C. Deamer) and Gertrud, who, with Mrs. Ophüls, survive him.

Dr. Ophül's published contributions to medical science were not so numerous as they would have been had his time not been taken up so fully with teaching, laboratory analysis and administrative work in the public service and in the office of dean. Still, he made notable contributions to the knowledge of tuberculosis, amyloid substance, coccidioidal gran-



WILLIAM OPHÜLS.
1871–1933

uloma (it was he who established the fact that the organism is a mold), pseudotuberculosis, inflammation in the kidneys and the liver, and arteriosclerosis. In 1926 he published a critical analysis of the observations in 3,000 autopsies. During his progressive illness he was engaged in completing the manuscript of a textbook of pathology, which it is hoped will be published posthumously.

In the death of William Ophüls, Stanford Medical School has lost a great teacher; the medical profession, a clear-headed leader in better medical thought, and the scientific world, a capable investigator exceptionally well equipped for original work.

EMMET L. RIXFORD.
JAMES B. MCNAUGHT.

INDEX TO VOLUME 15

The asterisk (*) preceding the page number indicates an original article in the Archives. Author entries are made for original articles and society transactions. Subject entries are made for all articles. Book Reviews, Obituaries, and Society Transactions are indexed under these headings in their alphabetical order under the letters B, O and S, respectively.

Abdomen, massive intra-abdominal hemorrhage in new-born, 140
Abnormalities: See Anomalies and Deformities
Abortion, agglutination test in diagnosis of infectious abortion in cattle, 301
fatal arbor vitae poisoning through employment of twigs as an abortifacient, 590
inheritance of resistance and susceptibility to infectious abortion, 449
soap necrosis of pregnant uterus, 591
Abscess: See under names of organs and regions
Acid, lactic; accidental, fatal lactic acid poisoning, 590
Acromegaly, changes in vertebral column in, 292
Actinobacillus bacteremia, 576
Actinomycosis of brain, 452
of hypophysis cerebri and actinomycotic leptomeningitis, 725
Adamantinoma of jaw with aspiration metastases to right lung, 586
Adams, L. J.: Experimental chronic nephritis produced by radium, *465
Adenosarcoma, relation of so-called adenosarcoma in kidney to neuroblastoma, 158
Adipose Tissue: See Fat
Adiposogenital Syndrome: See under Pituitary Body
Adrenals: See Suprarenals
Agglutination and hemolysis in fish, 303
group specific differentiation of human organs, 302
hemagglutination and hemolysis in Macacus cynomolgus and Simia Rhesus, 304
hyperproteinemia as cause of autohemagglutination, 858
physicochemical qualities of isohemoagglutinogens, 732
species agglutination, 304
Alcohol poisoning, changes in Golgi apparatus in, 285
Alcoholism, cerebral apoplexy following alcoholic excess, 312
Allergy: See Anaphylaxis and Allergy
Amebiasis, pathology of amebiasis in carriers, 575
American Medical Association, scientific exhibit at Milwaukee, 132
Ammonia, suicidal poisoning with ammonia, 591
Amyloid disease, retention of congo red in, *238
localized amyloidosis with macroglossia, 723
Anaerobic Bacteria: See under Bacteria
Anaphylaxis and Allergy: immunological behaviour of second protein (livetin) of hen's egg yolk, 299
influencing anaphylactic symptoms and shock with organ extracts, 729
mechanism and prophylaxis of anaphylactic shock, 731
passive transference of urticarial hypersensitiveness to fungus extracts, 301
primary toxicity of lens and anaphylactic experiment, 303
Anaphylaxis and Allergy—Continued
removal of anaphylactogenic properties of serum, 730
rôle of leukocytolysines of spleen in anaphylactic shock, 728
Anemia, erythroblastic, 140
macrocytic and hemolytic anemia, 849
marrow hyperplasia and hemoglobin reserve in anemia due to bleeding, 432
racial or familial anemia of children, 141
size of erythrocytes in secondary anemia, 163
Aneurysm, aortic, producing pulmonary stenosis and bundle-branch block, 139
Brucella meningo-encephalitis with mycotic aneurysm, 575
degenerative mesa-aortitis without syphilis with a dissecting aneurysm in a 20 year old woman, 162
posttraumatic aneurysm of basal cerebral artery, 312
traumatic aneurysms of basal cerebral arteries, 875
Angioma; angiomatous malformations of brain; report of 2 cases of angioma racemosum, *340
angiomatosis of retina (von Hippel and Lindau's disease), 440
Aniline, fatal poisoning with aniline, 311
workers, occupational carcinoma in, 309
Anomalies and Deformities: See also under names of diseases, organs and regions
causative organism in infectious ectromelia, 150
persistent truncus arteriosus and congenital absence of one kidney with other developmental defects, *51
Antibodies: See Antigens and Antibodies
Antigens and Antibodies; action of extracts of feces on bacterial blood antigens and on human erythrocytes, 303
distribution of arensic containing antigen in organism, 871
group-specific differentiation of human organs, 869
isolation of group-specific antigens of human red blood cells, 869
lipoid antigens and antibodies in malignancy and pregnancy, 302
method for separating antibodies from serum proteins (protein-free antibody), 584
site of formation of antibodies in rabies, 585
specificity of antibodies against lipoids, 868
Antiserums: See Serums
Aorta, Aneurysm: See Aneurysm
calcification of human aorta and ergosterol, 861
fatal rupture of aorta from apparently minor causes, 440
transient thickening of aortic intima in childhood, 288
traumatic shock syndrome following rupture of aorta and multiple fractures, 880
Aortitis, degenerative mesa-aortitis without syphilis with a dissecting aneurysm in a 20 year old woman, 162
relations between syphilitic aortitis and atherosclerosis, 573
suspected poisoning: death from rheumatic aortitis, 311
syphilitic enlargement of aortic valve in, 572
valvular changes in syphilitic mesa-aortitis, 441

Apoplexy: See Brain, hemorrhage
Apparatus: See also Instrument
live steam inspissator attachment for autoclave, *539
Appendix, primary epithelial tumors of vermiform appendix; observations by silver impregnation, *78
pseudomyxoma of peritoneum of appendical origin, 735
unsuspected hemochromatosis with mucocele of appendix, 750
Arbor vitae poisoning, fatal arbor vitae poisoning through employment of twigs as an abortifacient, 590
Arecaline poisoning, 3 cases of, 312
Argentophile fibers in miliary tuberculosis, 853
Argyria: See under Silver
Arsenic, absorption and distribution of arsenic in human body following its external application, 459
distribution of arsenic containing antigen in organism, 871
methods for microchemical demonstration of arsenic in tissues, *789
Arsphenamine, differences in distribution of chemotherapeutic agents in mice depending on site of injection, 286
Arteries: See also Aneurysm; Aorta; Arteriosclerosis; Blood pressure; Embolism
cerebral, traumatic aneurysms of basal cerebral arteries, 875
congenital calcification of arteries and other tissues, 438
coronary, unusual lesions, 876
experimental rupture of elastic tissue of arteries and lipoid infiltration, 280
necrotizing arteritis and subacute glomerulonephritis in gonococcic endocarditis; toxic origin of periarteritis nodosa, *35
pulmonary; primary sclerosis and obliterative endarteritis of pulmonary artery, 855
renal, acute glomerulitis following injection of streptococcus viridans into renal artery, 718
renal; traumatic rupture of left renal artery without injury to kidney, 310
tuberculosis of systemic arteries with fatal rupture, 852
Arteriosclerosis, experimental, 569
incidence and severity of arteriosclerosis in 500 autopsies, 876
relation of suprarenals to hypertension and arteriosclerosis, 436
Arthritis, chronic purulent polyarthritis, 281
relation of chronic polyarthritis to acute rheumatic infection, 282
subcutaneous nodules in chronic arthritis, 287
Asbestosis: See Pneumoconiosis
Ascaris, lungs of children with ascaris, 862
Aschheim-Zondek pregnancy test, Friedman modification of, 160
Atherosclerosis, studies in, 142
relations between syphilitic aortitis and atherosclerosis, 573
Autoclave, a live steam inspissator attachment for autoclave, *539
Autopsies; postmortem examination of bodies of sovereign bishops of Würzburg during the seventeenth and eighteenth centuries, 723

B C G: See under Tuberculosis
Bacillus: See Bacteria
Bacteremia, appearance and significance of bacteremia in diphtheria, 297
Bacteria: See also Dysentery bacilli; Tubercle Bacilli; etc.
abortus, mechanism of infection particularly in mice with Bacillus abortus, 727
abortus, vaccination of mice against Bacillus abortus, 731
acid-fast bacilli, 453
acid-fast; cellular reactions to lipoid fractions from acid-fast bacilli, 864
Bacteria—Continued
anaerobic; filter-passing anaerobic bacteria of nose and throat in health and in colds, 148
anaerobic; respiratory metabolism and tissue respiration in experimental anaerobic infection, 137
Brucella abortus; evidence of Brucella abortus infection in slaughterhouse men, 866
Brucella abortus in tonsils, 576
Brucella meningoencephalitis with mycotic aneurysm, 575
Brucella; metabolism studies on Brucella group, 449
constant temperature water baths, 739
Corynebacteria; diphtheroid bacillus and streptococcus in acute endocarditis, 574
kinetics of bacterium-bacteriophage reaction, 578
Lactobacillus acidophilus in adults, 146
mycobacteria, development of non-acid fast forms, 577
mycoides, dissociation and life cycle of, 863
Pasteurella pseudotuberculosis, 445
Pastuerella tularensis, induction of avirulence in Pasteurella tularensis, 581
pseudotuberculosis, further studies on B. pseudotuberculosis, 445
vibrios from intestinal tract of gray rat, 446
Bacteriophage, active and passive immunization against bacteriophage, 868
critique of serial dilution method for quantitative determination of bacteriophage, 866
effect of bacteriophage on Forssman and human blood antigens in B. paratyphoid B and in B. dysenteriae Shiga, 303
electrical charge of, 577
heat inactivation of antistaphylococcus bacteriophage, 580
"killing" of bacteria by bacteriophage, 295
kinetics of bacterium-bacteriophage reaction, 578
method for quantitative determination of bacteriophage, 578
relationship of bacteriophage to diseases of laboratory animals, 449
Bacteriotropins, production of specific bacteriotropins in infections with hemolytic streptococci, 583
Barbital, brain lesions of acute barbital (veronal) poisoning, 159
Barium, detection of barium in human bones, 313
in animal bones, 313
Barnard, R. D.: Potentiometric determinations of malignant human and transplanted rat tumors, 169
Bartonella infection, function of spleen in Bartonella infection of white rat, 731
muris, isolation of, 864
Beaver, D. C.: Persistent truncus arteriosus and congenital absence of one kidney with other developmental defects, *51
Beck, J. S. P.: Multilocular cystic lymphangioma of spleen, *655
Bendien flocculation test in malignant conditions, 459
Beryllium, bone lesions in rats produced by substitution of beryllium for calcium in diet, *18
Bevan, E.: Congenital cardiac anomaly, 597
Bile Ducts, changes in extrahepatic bile ducts with age, 572
concentration and precipitation of bilirubin in gallbladder and bile ducts; experimental studies on cats and dogs, *818
ligation of common bile duct, 434
morphology of bile ducts in mechanical icterus, 290
Biliary disease, cholesterol of blood plasma in hepatic and biliary diseases, 857
Bilirubin, concentration and precipitation of bilirubin in gallbladder and bile ducts; experimental studies on cats and dogs, *818

Bladder calculus; argyria with gigantic stone in bladder, 751
Blastomycosis, systematic, 576
Blood: See also Erythrocytes; Hemoglobin; Leukocytes
action of extracts of feces on bacterial blood antigens and on human erythrocytes, 303
capillaries, contractility of (anatomic researches), 434
cell-plasma ratio and estimations of hemoglobin by cell concentration, *843
changes produced in blood picture by removal of normal mammalian spleen, 431
cholesterol of blood plasma in hepatic and biliary diseases, 857
copper and non-hemoglobinous iron contents of blood serum in disease, 858
correlation of certain blood diseases on hypothesis of bone marrow deficiency or hypoplasia, 848
cultures of apparently healthy persons, 581
cysts, origin of epithelium-lined blood cysts (chocolate cysts) from graafian follicle and its derivatives, 288
diastase in cancer, *834
donors, 847
effect of bacteriophage on Forssman and human blood antigens in B. paratyphoid B and in B. dysenteriae Shiga, 303
effect of experimental splenectomy on blood platelets and bone marrow, 284
group ferments, 869
group; heredity of agglutinogens M and N of Landsteiner and Levine, 301
group, is there a relation between blood group and mental diseases? 154
group; so-called subgroups of A, 153
grouping with polluted and physically influenced blood samples, 313
group-specific differentiation of human organs, 869
influence of plasma protein on chloride content of cerebrospinal fluid, 432
isolation of group-specific antigens of human red blood cells, 839
lipemia; variations in total blood lipid in alimentary lipemia, 431
lipids, variations in total blood lipid in alimentary lipemia, 431
lipoids; significance of plasma lipoids for suspension stability of blood, 860
maturing effect of roentgen rays on blood-forming cells, 717
micro-iodine determination of blood, 860
nonprotein sulphur in formed elements of blood, 861
pressure, relation of suprarenals to hypertension and arteriosclerosis, 436
protein; hyperproteinemia as cause of autohemagglutination, 858
quantitative distribution of blood, 136
relation of liver to infections of blood stream, 284
serum, chemical and physicochemical changes in blood serum following infection and immunization, 154
specificity of tissue and blood reaction, 289
stains, Takayama's solution in identification of blood stains, 161
transfusion, reactions to, 721
Böhmig, R.: Comparative histologic reactions in cutaneous lesions induced by streptococci in rabbits previously inoculated intracutaneously or intravenously, *611
Bones, barium in animal bones, 313
barium in human bones, detection of, 313
calcium metabolism and diseases of bone, 715
cancer metastases in bone with special reference to osteophytosis, 155
chemical and physical properties of bone in experimental scurvy, 860
effect of vitamin D on bone, 435
fragility; absence of osteoporosis demonstrated chemically in clinical hyperthyroidism, 431
Bones—Continued
fragility; experimental and fibrous ostitis in dogs, 720
growth; skeletal changes in osteogenesis imperfecta, 854
injuries to bones of human cadavers by rodents, 158
lesions in rats produced by substitution of beryllium for calcium in diet, *18
marrow, correlation of certain blood diseases on hypothesis of bone marrow deficiency or hypoplasia, 848
marrow, effect of experimental splenectomy on blood platelets and bone marrow, 284
marrow hyperplasia and hemoglobin reserve in anemia due to bleeding, 432
osteopoikilosis: disseminated condensation of bones, 288
Paget's disease of bone, *83
sarcoma, causal relation of trauma to, 158
sarcoma, experimental, 881
saw, double-bladed, 314
tumors with thyroid structure, 306
Book Reviews:
American Illustrated Medical Dictionary; A Complete Dictionary of Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, etc., with the Pronunciation, Derivation, and Definition; W. A. Newman Dorland, 608
Calcium Metabolism and Calcium Therapy; A. Cantarow, 752
Cardiac Output of Man in Health and Disease; Arthur Grollman, 173
Coronarkreislauf, Physiologie, Pathologie, Therapie; M. Hochrein, 461
Endocrine Medicine; W. Engelbach, 463
Final Report of Commission on Medical Education, 463
Handbook of Experimental Pathology; G. Wagoner and R. P. Custer, 319
Heart Rate; E. P. Boas and E. F. Goldschmidt, 320
History of Dermatology; W. A. Pusey, 607
Individuality of Blood in Biology and in Clinical and Forensic Medicine; L. Lattes, 318
Intracranial Tumors; P. Bailey, 885
Lehrbuch der Histologie und Histogenese; J. Schaffer, 608
Neuropathology: Anatomical Foundation of Nervous Diseases; W. Freeman, 753
Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System; H. Cushing, 607
p_H and Its Practical Application; F. L. LaMotte, W. R. Kenny and A. B. Reed, 462
Physical Chemistry for Students of Biology and Medicine; D. I. Hitchcock, 606
Practical Hematological Diagnosis; O. H. P. Pepper and D. L. Farley, 885
Report of Medical Research Council for the Year 1931-32, 609
Sex and Internal Secretions: A Survey of Recent Research; E. Allen et al., 752
Spirochétose méningée; J. Troisier and Y. Bouquien, 609
Books Received, 174, 610, 754
Bottcher and Charcot-Leyden crystals, identity of, 861
Boxing, death from shock during boxing match, 875
Brain, actinomycosis of brain, 452
angiomatous malformations of brain; report of 2 cases of angioma racemosum, *340
calcareous concretions of, 444
diffuse demyelinization of brain (Schilder's disease), 291
emulsion, effects of injection of normal brain emulsion into rabbits, 149

Brain—Continued
hemorrhage, cerebral apoplexy following alcoholic excess, 312
hemorrhage; microscopic cerebral hemorrhage in stillbirths and new-born deaths, 286
hemorrhage, traumatic late apoplexy, 159
histologic characteristics of basal cerebral arteries, 291
malformations, inner and middle ear in cases of, 574
narcosis and oxidations of brain, 859
peptic ulcers and interbrain, 433
phosphatid content of brain in Niemann-Pick disease, 284
phosphatid degeneration of cells of brain, liver and spleen in Niemann-Pick's disease, 861
tumors, diagnosis of intracranial tumors by supravital technic, 587
Bread, influence of rye and of wheat bread on rats and mice, 726
Breast, cancer; mammary ducts in carcinoma of mammary glands, 307
changes in mammary gland produced by removal of nipple, 158
chorion epithelioma of testicle with metastases, gynecomastia and pregnancy reaction (Friedman), 316
chorionepithelioma of testis with abnormal development of male breast, 307
organic phosphorus compounds and phosphatase in, 862
roentgenograms of breast and its lesions and their histologic correlation, 163
time at which casein begins to be formed in breast during pregnancy, 168
tumors, intracellular fat in, 872
Brebner, W. B.: Purification of poliomyelitic virus, *221
Brewer, J. I.: Implantation and structure of human ovum near seventeenth day (primitive streak stage), 879
Bright's Disease: See Nephritis
Brink, J. R.: Leiomyosarcoma of jejunum, 316
Bronchiectasis, pathology of bronchiectasis, *357
Bronchus, desquamation of bronchial epithelium in new-born and young infants, 311
Brucella: See under Bacteria
Brunschwig, A.: Experimental bone sarcoma, 881
Bundle of His: See under Heart
Burman, M. S.: Fluorescence of cartilage exposed to filtered ultraviolet radiation, *537
Burns, changes in mucous membranes of upper respiratory tract in death by burning, 460
Button fever, "fièvre boutonneuse," 867

Cadavers, injuries to bones of human cadavers by rodents, 158
Calcification; calcareous concretions of brain, 444
congenital calcification of arteries and other tissues, 438
Calcium, bone lesions in rats produced by the substitution of beryllium for calcium in diet, *18
metabolism, relationship of, to diseases of bone, 715
salts, staining of insoluble calcium salts in tissues, 740
Cancer: See also Sarcoma; Tumors, etc.; and under names of organs and regions
altered behavior of red cells of cancerous subjects after exposure to fluorescing substances, 457
attempts at early diagnosis of cancer by capillary-dynamic methods, 155
Bendien flocculation test in malignant conditions, 459
blood diastase in cancer, *834
cholesterol content of carcinoma lipoid, 860
combining affinities in bacterial variation and carcinogenesis, 587
Cancer—Continued
comparative investigations of different reactions for carcinoma, 157
complement fixation in, 874
complement-fixing antibodies in carcinomatous rabbits, 874
implantation and contact metastases of malignant tumors, 873
in Cochin China, 306
lipoid antigens and antibodies in malignancy and pregnancy, 302
metastases in bone with reference to osteophytosis, 155
mortality in Charkow (U. S. S. R.), 734
Nordhoff-Jung cancer prize, 279
occupational carcinoma in aniline workers, 309
potentiometric determinations of malignant human and transplanted rat tumors, 169
primary malignant tumors of serous cavities, 458
rat carcinoma and injected colloidal platinum, *796
relationship between embryonal and carcinomatous tissue, 456
research and serology, 307
Research Institute, Copenhagen, 132
serologic reactions in malignant disease, 457
structure of malignant tumor cell, 734
Weiss coagulofloculation test of malignancy, *393
Cannon, P. R.: Some changing emphases in study of infection and resistance, 164
Capillary endothelium, potentialities of, 138
Carbon Monoxide, effect of carbon monoxide and other agents upon rate of tumour growth, 305
histologic changes in brain in experimental chronic illuminating gas poisoning, 159
stimulation of muscle respiration by, 716
Cartilage, fluorescence of cartilage exposed to filtered ultraviolet radiation, *537
Casein, time at which casein begins to be formed in breast during pregnancy, 168
Cerebrospinal Fluid, diastase content in syphilis, 739
influence of plasma protein on chloride content of, 432
new method of occipital puncture in rabbit, 161
Charcot-Leyden and Böttcher crystals, identity of, 861
Chemotherapy, differences in distribution of chemotherapeutic agents in mice depending on site of injection, 286
Chenopodium, fatal medicinal poisoning with chenopodium, 590
Chinese, disease among Chinese and geographic pathology, 436
Chlorides, dilution of chlorides in body fluids as a sign of drowning in fresh water, 738
Chocolate cysts, origin of epithelium-lined blood cysts (chocolate cysts) from graafian follicle and its derivatives, 288
Cholelithiasis: See Gallbladder, calculi
Cholera, histology of acute hog cholera, 856
histologic studies on hog cholera, 570
Cholesteatoma, epidermoidal cholesteatoma in cranial cavity of horse, 308
Cholesterol, antigenic qualities of cholesterol and of its derivatives, 869
content of carcinoma lipoid, 860
histologic diagnosis of tumors by means of histochemical demonstration of cholesterol, 155
masking of antigenic effects of haptens in vitro and in vivo inhibition of immunogenic effect of cholesterol by lecithin, 154
metabolism of liver, 437
production of "ball" phenomenon in colloidal solutions of cholesterol and in cholesterolized lipoid mixtures by hydrochloric acid and sodium chloride, 732

Cholesterol—Continued
relation of cholesterol to indophenol-oxydase reaction, 861
Chondrosarcoma, metastasizing chondrosarcoma of coronoid process of mandible, *649
Chor, H.: Attempt to transmit poliomyelitis to splenectomized guinea-pigs, *387
Chorio-allantoic membrane, vaccinal infection of chorio-allantoic membrane of chick embryo, 446
Chorionepithelioma of testis, 589
of testis with abnormal development of male breast, 307
Christian-Schüller Syndrome: See Schüller-Christian Syndrome
Christianson, O.: Nasopharyngeal carcinoma, 879
Chromaffin tumors of sympathetic system, 2 cases, 455
Cinchophen, effect of cinchophen on albinic rat, *490
poisoning in diabetic with induction of hypoglycemia, 310
toxic cirrhosis of liver due to cinchophen, 309
Clark, J. H.: Development of a pathologic laboratory in Philadelphia General Hospital, 594
Clostridium: See under Bacteria
Coccidiosis of liver in rabbits; experimental study of excystation of oocysts of Eimeria stiedae, *175
of liver in rabbits; experimental study of histogenesis of coccidiosis of liver, *516
of liver in rabbits; experimental study on mode of infection of liver by sporozoites of Eimeria stiedae, *330
Coggeshall, L. T.: Pathogenesis of experimental pneumococcic lobar pneumonia in dogs, 878
Colds, filter-passing anaerobic bacteria of nose and throat in health and in colds, 148
Colloid, tissue reaction to colloid and lipoids from human thyroid gland, *244
Colloidal platinum, rat carcinoma and injected colloidal platinum, *796
Colon, experimental inflammation of colon; relationship of mucus production in goblet-cells to Golgi apparatus; mitochondral changes, 433
Copper and "active" iron content of tissues, 171
sulphate, suicidal copper sulphate poisoning, 591
Corpus callosum, traumatic destruction of corpus callosum without fracture of skull, 573
Craniorachischisis, skeletal conditions in, 571
Cranium, cranial hyperostosis, associated with an overlying fibroblastoma, 144
epidermoidal cholesteatoma in cranial cavity of horse, 308
malformation of skull in cases showing a naso-orbital encephalocele, 572
malformations of, inner and middle ear in, 574
skeletal conditions in craniorachischisis, 571
Crawford, B. L.: Shock syndrome in mercuric chloride poisoning, *509
Custer, R. P.: Origin of megakaryocytes in extramedullary loci, 595
Cutler, O. I.: Time at which casein begins to be formed in breast during pregnancy, 168
Cystadenoma of lymphatic trunk, 872
Cystitis: See Bladder, inflammation
Cysts, calcified cysts of kidney, 145
cholesteatomatous cyst of lower jaw, 722
experimental fibrous osteodystrophy in dog with pseudotumors and cysts of jaw, 568
fate of surface epithelium transplanted into deeper tissues and relation of such epithelium to epithelial cysts, 134

Davenport, H. A.: Staining of oligodendroglia and microglia in pyroxilin (celloidin) sections, 315
Davis, M. E.: Histologic changes in rabbits and in dogs following intravenous injection of thorium preparations, *27
Death, influence of changes in weather on approaching death, 280
statistical and theoretical data on unexpected death from natural causes, 312
Degeneration, nature of cloudy swelling, 440
Dermoid cysts, fats in dermoid cysts and their biologic significance, 861
Deutsch, E.: Concentration and precipitation of bilirubin in gallbladder and bile ducts; experimental studies on cats and dogs, *818
Dextrose, conversion of levulose to dextrose during absorption from intestine, 716
Diabetes, cinchophen poisoning in diabetic with induction of hypoglycemia, 310
insipidus in patient with tumor metastasis to hypophysis, 134
Diaphragm, histology and function of, 444
Dickson, J. G.: Chorion epithelioma of testicle with metastases, gynecomastia and pregnancy reaction (Friedman), 316
Diphtheria, anaphylaxis to diphtheria toxin from placental transmission of antitoxin, 153
appearance and significance of bacteremia in diphtheria, 297
bacillary immunity in, 729
immunity among black races, 154
percutaneous immunization against, 868
positive seroreactions for syphilis following injection of antidiphtheria serum, 585
renal changes in mixed diphtheritic and scarlatinal infection, 855
toxoid, precipitation of diphtheria toxoid by metallic salts, 583
Diphtheroid Bacillus: See Bacteria, corynebacteria
Diuretics, effect of diuretics on output of water by skin, 570
Dixon, H. M.: Multiple diverticula of jejunum, 162
Dopa reaction, melanoma studies, simple technique for Dopa reaction, 592
Dragstedt, L. R.: Ulcus acidum of Meckel's diverticulum, 168
Drowning, dilution of chlorides in body fluids as a sign of drowning in fresh water, 738
water in lungs of drowned animals, *828
Dudley, G. S.: Malignant tumors of thyroid gland, 743
Dunn, F. L.: Core drill (trephine) for postmortem exposure of accessory nasal sinuses, nasal passages, mouth and pharynx, *255
Duodenum, carcinoma, 308
injuries of stomach and duodenum by blunt violence, 310
Dyes: See Stains and Staining
Dysentery, action of toxin of Bacillus dysenteriae, 297
bacilli, biologic variability of, 726
bacilli, variability of dysentery bacilli and their etiologic identity, 727
effect of brilliant green on Eberthella dysenteriae, Sonne type, 294
effect of bacteriophage on Forssman and human blood antigens in B. paratyphoid B and in B. dysenteriae Shiga, 303

Ear, changes in middle and internal ear following chronic otitis media, 438
inner and middle ear in cases of malformations of brain and skull, 574
Ectodermal dysplasia, hereditary, 142
Ectodermoses: See Skin diseases
Ectromelia, causative organism in infectious ectromelia, 150
Edema, experimental edema from plasma protein depletion, 711

Eggs, lysozyme and flocculation phenomenon of chicken egg-white, 730
presence of tubercle bacilli in hen's eggs, 298
Egloff, W. C.: Experimental chronic nephritis produced by radium, *465
Eimeria stiedae, coccidiosis of liver in rabbits; experimental study on excystation of oocysts of Eimeria stiedae, *175
stiedae, mode of infection of liver by sporozoites of, *330
Electric accidents in mining, 460
Electrocardiogram: See under Heart
Ella Sachs Plotz foundation for Advancement of Scientific Investigation, 847
Elton, N. W.: Concentration and precipitation of bilirubin in gallbladder and bile ducts; experimental studies on cats and dogs, *818
Embedding material, a new embedding material, 160
Emboli, fate of endometrial emboli in venous circulation of rabbit, *1
physiopathology of arterial emboli of extremities, 850
studies of emboli in heart, 441
Encephalitis: See also Meningo-Encephalitis
periaxialitis; diffuse demyelinization of brain (Schilder's disease), 291
post-vaccinal, 286
Encephalocele, malformation of skull in cases showing a naso-orbital encephalocele, 572
Enchondroma, histology of malignant embryonic enchondroma, 736
Endamoeba histolytica, negative occult blood tests in carriers of endamoeba histolytica, 862
Endarteritis, primary sclerosis and obliterative endarteritis of pulmonary artery, 855
Endocarditis, acute endocarditis of pulmonic valve, 855
differential histology of syphilitic and non-specific chronic endocarditis of aortic valve, 439
diphtheroid bacillus and streptococcus in acute endocarditis, 574
lenta, biology of Streptococcus viridans in, 297
micrococcus siccus endocarditis, 446
necrotizing arteritis and subacute glomerulonephritis in gonococcic endocarditis, *35
Endometrium, fate of endometrial emboli in venous circulation of rabbit, *1
Endothelium, potentialities of capillary endothelium, 138
Eosinophile cell, some observations on, 853
Epinephrine: See Suprarenal Preparations
Epithelioma, chorion epithelioma of testicle with metastases, gynecomastia and pregnancy reaction (Friedman), 316
mucus-secreting cells in benign epitheliomas of skin, 307
Epithelium, fate of surface epithelium transplanted into deeper tissues and relation of such epithelium to epithelial cysts, 134
Erb, I. H.: Pathology of bronchiectasis, *357
Ergosterol and calcification of human aorta, 861
effect of viosterol on periosteum and experimental fracture, 718
experimental transmission of harmful effects of viosterol from mother to young, 139
Erysipelas, growth of erysipelas and scarlet fever streptococci on hemoglobin chocolate agar, 148
Erythrocytes, action of extracts of feces on bacterial blood antigens and on human erythrocytes, 303
size of erythrocytes in secondary anemia, 163
Erythroleukoblastosis: See Hematopoietic System
Erythroleukosis, so-called, in chickens, 457
Erythropoiesis in leukemia, 169
Exlax, poisoning by, 310
Extracts, Organ: See Organ Extracts
Eye, sarcoma of 455
Fat, staining of intracellular fat in tissue cultures, 740
Feces, action of extracts of feces on bacterial blood antigens and on human erythrocytes, 303
Ferguson, J. A.: Tissue reaction to colloid and lipoids from human thyroid gland, *244
Fever therapy; effect of short wave fevers on rabbits, 719
therapy; healing of experimental syphilis in rabbits by short wave fever, 864
Fibroblastoma, cranial hyperostosis associated with an overlying fibroblastoma, 144
Fibrosarcoma in wild rabbit, 872
"Fièvre boutonneuse," 867
Fink, E. B.: Gumma of hypophysis and hypothalamus, *631
Flocculation phenomenon, lysozyme and flocculation phenomenon of chicken egg-white, 730
Fluorescence of cartilage exposed to filtered ultraviolet radiation, *537
Fluoride poisoning, pathologic anatomy of, 875
Foot-and-mouth disease lesions in ear epidermis of inoculated guinea-pigs, 149
Formol detoxication of purified staphylococcal toxin, 451
Fracture, effect of viosterol on periosteum and experimental fracture, 718
traumatic shock syndrome following rupture of aorta and multiple fractures, 880
Friedman modification of Aschheim-Zondek pregnancy test, 160

Gallbladder, agnesia of, 573
calculi, etiology of, *698, 858
concentration and precipitation of bilirubin in gallbladder and bile ducts; experimental studies on cats and dogs, *818
"strawberry," pathogenesis of, 718
Gangrene, spontaneous, of extremities, 140
Gastro-intestinal tract, uremic ulceration and necrosis, 856
Gee's disease (idiopathic steatorrhoea), 849
Geschickter, C. F.: Tumors of suprarenal gland, *775
Glia: See Neuroglia
Gliomas, intranuclear "inclusion bodies" in gliomas, 589
histology, 735
peripheral, 586
Glomerulonephritis: See under Kidney
Glycol stearate, a new embedding material, 160
Goiter, desquamation of cells of follicular lining in exophthalmic goiter, 574
endemic, hematology of, 721
histology of heart in exophthalmic goiter, 571
iodine content of food substances and incidence of goiter, 860
occurrence of antigoitrous substances in plants, 720
Golgi apparatus, changes in alcohol poisoning, 285
Gonococcus, necrotizing arteritis and subacute glomerulonephritis in gonococci endocarditis; toxic origin of periarteritis nodosa, *35
qualities of filtrates of gonococcus cultures, 868
Gonzales, T. A.: Manual strangulation, *55
Graham, A.: Tumors of thyroid gland; pathologic aspects, 741
Granulosa cell tumor of ovary, 747
Gross, A.: A live steam inspissator attachment for autoclave, *539
Growth, aberrant growth in regenerating claws of hermit crab under influence of sulphydryl: their relation to neoplasia, *675
Gumma of hypophysis and hypothalamus, *631
Gums, symmetrical hypertrophy of gums, 725
Guyer, M. F.: Rat carcinoma and injected colloidal platinum, *796
Gynecomastia: See under Breast

Hardgrove, M. A. F.: Retention of congo red in amyloid disease, *238
Harmon, P. H.: Experimental bone sarcoma, 881
Heart: See also Endocarditis; Myocarditis
aneurysm of aorta producing pulmonary stenosis and bundle-branch block, 139
anomaly, congenital, 597
block, anatomical causes of, 290
destruction of left half of bundle of His without alteration of ventriculogram, 850
disease, arteriolar studies in patients with hypertensive heart disease without hypertension, 142
disease, incidence and distribution of age of death in rheumatic heart disease, 715
dynamics of cardiac hypertrophy and dilatation, 569
effect of lipoids on surviving heart of frog, 283
enlargement of aortic valve in syphilitic aortitis, 572
fenestrated hammock-like structure in left cardiac atrium; review of literature and report of case, *8
fusion of chordae tendineae and papillary muscles, 290
histology of heart in exophthalmic goiter, 571
persistent truncus arteriosus and congenital absence of one kidney with other developmental defects, *51
polypoid tumors of left auricle of heart, 872
pulmonary insufficiency, pathology of, 435
rupture with perforation of interventricular septum, 139
valvular changes in syphilitic mesaortitis, 441
Hellwig, C. A.: Histologic changes in thyroid of rabbit following injection of urine, *321
Helpern, M.: Necrotizing arteritis and subacute glomerulonephritis in gonococcic endocarditis; toxic origin of periarteritis nodosa, *35
Helwig, F. C.: Fenestrated hammock-like structure in left cardiac atrium; review of literature and report of case, *8
Hemagglutination: See Agglutination
Hemangioblastomas, multiple hemangioblastomas of spinal cord with syringomyelia and cysts of pancreas and kidney (Lindau's disease), 604
Hemangio-endothelioma, so-called, of liver, 156
Hemato-encephalic barrier, effect of experimental hepatic damage on, 717
Hematopoietic System; fetal erythroleukoblastosis with fatal icterus neonatorum, 722
Hemochromatosis, 2 cases of human pseudotuberculosis associated with hemochromatosis, 725
unsuspected hemochromatosis with mucocele of appendix, 750
Hemoglobin, cell-plasma ratio and estimations of hemoglobin by cell concentration, *843
marrow hyperplasia and hemoglobin reserve in anemia due to bleeding, 432
Hemolysis and agglutination in fish, 303
hemagglutination and hemolysis in Macacus cynomolgus and Simia Rhesus, 304
Heparin, effect of prothrombin and heparin on proliferation and differentiation of tissues in vitro, 851
Hepatitis: See Liver
Hick, F. K.: A suprarenalin-producing pheochromocytoma of suprarenal gland; report of case, *665
Tumors of suprarenal cortex with reports of 3 cases of carcinoma and a lipoma, 881
Hodgkin's Disease: See Lymphogranuloma
Hueper, W. C.: Capillary-like formations in cultures of blood leukocytes, 162
Hunt, H. D.: Pulmonary varix with spontaneous rupture and death; report of case, *227
Hydrocephalus, congenital, 442
Hydrophobia: See Rabies
Hypersensitiveness: See Anaphylaxis and Allergy
Hypertension: See Blood pressure, high
Hyperthyroidism: See under Thyroid
Hypothalamus, gumma of hypophysis and hypothalamus, *631

Icterus: See Jaundice
Illuminating Gas: See Carbon Monoxide
Immunity, acquired immunity in plants induced by grafting, 730
active immunity to local skin reactivity to bacterial filtrates 151
significance of thrombozytobarine as a defensive mechanism in infection, 728
Immunization, chemical and physicochemical changes in blood serum following infection and immunization, 154
of chimpanzees with human blood, 152
Indophenol-oxydase reaction, relation of cholesterol to indophenol-oxydase reaction, 861
Infants, massive intra-abdominal hemorrhage in new-born, 140
microscopic cerebral hemorrhage in stillbirths and newborn deaths, 286
Infection, changing emphases in study of infection and resistance, 164
chemical and physicochemical changes in blood serum following infection and immunization, 154
mixed and secondary infection, 297
respiratory metabolism and tissue respiration in experimental anaerobic infection, 137
Inflammation, lymph pressures in sterile inflammation, 432
pathologic physiology of inflammation, 134
Influenza, immunity to swine influenza, 300
Inspissator, a live steam inspissator attachment for autoclave, *539
Instrument: See also Apparatus
core drill (trephine) for postmortem exposure of accessory nasal sinuses, nasal passages, mouth and pharynx, *255
double-bladed saw for bone, 314
Insulin, kataphoresis of insulin; insulin-glucose reaction in vitro, 859
protection of insulin by antiproteases and its absorption from intestine, 719
Intestine, automobile rupture of intestines, 737
conversion of levulose to dextrose during absorption from intestine, 716
diverticula; ulcus acidum of Meckel's diverticulum, 168
enterogenous cysts and diverticula, 172
invasion of wall of intestine by Trichomonas hominis, 446
protection of insulin by antiproteases and its absorption from intestine, 719
serologic analysis of intestinal mucosa, 870
vibrios from intestinal tract of gray rat, 446
Intranuclear bodies; intracranial inclusions in human nerve cells in variety of diseases, 570
Iodine content of food substances and incidence of goiter, 860
micro-iodine determination of blood, 860
Iron, copper and "active" iron content of tissues, 171
Islands of Langerhans: See Pancreas
Isohemo-Agglutination: See Agglutination

Jackson, C. M.: Weights of various organs in adult rat after inanition with or without dietary accessories, *636
Jacobsen, V. C.: Fate of endometrial emboli in venous circulation of rabbit, *1
Lymphoblastoma of spleen with splenectomy, 748
Jacobson, S. A.: Bone lesions in rats produced by substitution of beryllium for calcium in diet, *18
Myeloid leukemia with osteosclerosis, 602
Jaffe, H. L.: Comparative anatomy of semilunar cartilages of knee: normal presence of bone in menisci of some animals, 599
Paget's disease of bone, *83

Jaffé, R. H.: Erythropoiesis in leukemia, 169
Jamaica ginger, jake paralysis following ingestion of Jamaica ginger extract adulterated with tri-ortho-cresyl phosphate, 718
Jaundice, fetal erythroleukoblastosis with fatal icterus neonatorum, 722
morphology of bile ducts in mechanical icterus, 290
Jaw, adamantinoma of jaw with aspiration metastases to right lung, 586
changes in teeth and jaws in experimental scurvy, 851
cholesteatomatous cyst of lower jaw, 722
experimental fibrous osteodystrophy in dog with pseudotumors and cysts of jaw, 568
metastasizing chondrosarcoma of coronoid process of mandible, *649
Jejunum, leiomyosarcoma of, 316
multiple diverticula of, 162
Jones, H. O.: Implantation and structure of human ovum near seventeenth day (primitive streak stage), 879
Jones, R. A.: Metastasizing chondrosarcoma of coronoid process of mandible, *649
Jurisprudence, medical; a new medicolegal journal, 567
present status and future development of legal medicine in United States, *542

Karpovich, P. V.: Water in lungs of drowned animals, *828
Keratitis, nonspecific orchitis and keratitis in experimental syphilis, 147
Kerosene poisoning in children, 310
Kidney, absence; persistent truncus arteriosus and congenital absence of one kidney with other developmental defects, *51
acute glomerulitis following injection of streptococcus viridans into renal artery, 718
calcified cysts, 145
carcinoma, squamous cell, with complete infarction of kidney, as sequel to carcinomatous thrombosis of renal artery, 144
changes in mixed diphtheritic and scarlatinal infection, 855
effect of roentgen irradiation on, 568
experimental chronic nephritis produced by radium, *465
hyaline excretion droplets in kidney, 290
multiple hemangioblastomas of spinal cord with syringomyelia and cysts of pancreas and kidney (Lindau's disease), 604
necrotizing arteritis and subacute glomerulonephritis in gonococcic endocarditis; toxic origin of periarteritis nodosa, *35
peculiar form of nephritis associated with acquired syphilis, 289
plastic studies in abnormal renal architecture; two architectural units in chronic Bright's disease and their possible functional significance, *755
relation of so-called adenosarcoma in kidney to neuroblastoma, 158
review of literature on special physiology of, 568
weight, body size and renal function, 857
Kilduffe, R. A.: Weiss coagulo-flocculation test of malignancy, *393
Klinck, G. H., Jr.: Argyria with gigantic stone in bladder, 751
Pulmonary varix with spontaneous rupture and death; report of case, *227
Unsuspected hemochromatosis, with mucocele of appendix, 750
Knee, comparative anatomy of semilunar cartilages of knee; normal presence of bone in menisci of some animals, 599
Krumbhaar, E. B.: Size of erythrocytes in secondary anemia, 163
Kushner, J. I.: Cell-plasma ratio and estimations of hemoglobin by cell concentration, *843

Laboratory, development of a pathologic laboratory in Philadelphia General Hospital, 594
Lactic Acid: See Acid, lactic
Lactobacilli: See under Bacteria
Laing, G. H.: Leiomyosarcoma of jejunum, 316
Larynx, anatomy and pathology of laryngeal ventricle, 293
fractures by direct violence, 738
multiple papillomata with aerial metastases to lungs, 585
Lead poisoning, psychopathologic symptoms in, 874
Lebowich, R. J.: Granulosa cell tumor of ovary, 747
Lecithin, masking of antigenic effects of haptens in vitro and in vivo inhibition of immunogenic effect of cholesterol by lecithin, 154
Lederer, M.: Effect of cinchophen on albinic rat, *490
Legal medicine, present status and future development of legal medicine in United States, *542
Leiomyosarcoma of jejunum, 316
Lens, primary toxicity of lens and anaphylactic experiment, 303
Leprosy, dissociation of mycobacterium leprae, 862
Leptomeningitis, actinomycosis of hypophysis cerebri and actinomycotic leptomeningitis, 725
Leukemia, chronic leukemic reticulo-endotheliosis, 724
erythropoiesis in, 169
monocytic, 145
mouse, continuity of cell lineage in transmission lines of lymphatic leukemia, *198
mouse, studies on, 720
myeloid, with osteosclerosis, 602
transmission of chicken leukosis to chicks, 286
Leukocytes, capillary-like formations in cultures of blood leukocytes, 162
rôle of leukocytolysines of spleen in anaphylactic shock 728
Leukocytolysines: See Leukocytes
Levine, V.: Angiomatous malformations of brain; report of 2 cases of angioma racemosum, *340
Levulose, conversion of levulose to dextrose during absorption from intestine, 716
Lewis, J. H.: Time at which casein begins to be formed in breast during pregnancy, 168
Lillie, R. D.: Metastasizing chondrosarcoma of coronoid process of mandible, *649
Lindau's disease, multiple hemangioblastomas of spinal cord with syringomyelia and cysts of pancreas and kidney (Lindau's disease), 604
Linitis, syphilitic, plastic, 721
Lipemia: See under Blood
Lipoid antigens and antibodies in malignancy and pregnancy, 302
cellular reactions to lipoid fractions from acid-fast bacilli, 864
cholesterol content of carcinoma lipoids, 860
effect of lipoids on surviving heart of frog, 283
histiocytosis; report of case with diagnosis by biopsy, *193
histochemical differentiation of diseases characterized by lipoid infiltration of cells, 292
quantitative conditions of antigen-antibody reactions of lipoids, 869
specificity of antibodies against lipoids, 868
tissue reaction to colloid and lipoids from human thyroid gland, *244
Lipoma of suprarenal cortex, 881
lipomatosis of pancreas in a child, 444
Liver, acute yellow atrophy, copper in liver in, 857
autolysis, 861
capillary circulation of, reflex control of, 283
carcinoma, primary, 589
cholesterol metabolism of, 437
cholesterol of blood plasma in hepatic and biliary diseases, 857

Liver—Continued
coccidiosis of liver in rabbits; experimental study of histogenesis of coccidiosis of liver, *516
coccidiosis in rabbits; experimental study on excystation of oocysts of Eimeria stiedae, *175
coccidiosis of liver in rabbits; experimental study on mode of infection of liver by sporozoites of Eimeria stiedae, *330
effect of experimental hepatic damage on hemato-encephalic barrier, 717
effect of radium emanation on histiocyte in liver of white rat, 287
experimental hepatitis and cirrhosis produced by thorium dioxide, 850
experimental liver disease produced by x-ray irradiation of exposed organ, 848
experimental tuberculotoxic lesions of liver, 452
function, studies on, 716
hemangio-endothelioma, so-called, 156
phosphatide degeneration of cells of brain, liver and spleen in Niemann-Pick's disease, 861
pseudotuberculous necroses of human liver, 445
relation of liver to infections of blood stream, 284
toxic cirrhosis due to cinchophen, 309
Livetin, immunological behaviour of second protein (livetin) of hen's egg yolk, 299
Locke, A.: Copper and "active" iron content of tissues, 171
Long, E. R.: Inflammatory reaction in tuberculosis, 598
Lund, E. M.: Plastic studies in abnormal renal architecture; two architectural units in chronic Bright's disease and their possible functional significance, *755
Lund, H.: Degenerative mesaortitis without syphilis with a dissecting aneurysm in a twenty year old woman, 162
Uusual coronary lesions, 876
Lung, cancer, frequency of, 157
cancer, occupational incidence of primary lung cancer, 306
cancer, primary, metastasis of, 459
cysts; polycystic disease of lungs, 853
fatal fibrosis of lungs due to inhalation of radium, 571
neuro-epithelioma, 590
of children with ascaris, 862
pneumonia from aspiration of fat and oil in lungs, 288
thickening of pulmonary apex and splenic capsule, 291
Tuberculosis: See Tuberculosis, pulmonary
tumor, primary, malignant, 157
varix with spontaneous rupture and death, report of case, *227
water in lungs of drowned animals, *828
Lymph pressures in sterile inflammation, 432
lymphatic trunk; cystadenoma of lymphatic trunk, 872
nodes, structure of lymph nodes in relation to their function, 724
Lymphangioma multilocular cystic lymphangioma of spleen, *655
Lymphatism, status lymphaticus, causes of death in, 715
Lymphoblastoma of spleen with splenectomy, 748
Lymphocytes, effect of lymphocytosis from chick embryo extract on tuberculosis in rabbits, 448
transformational potencies of lymphocyte, 292
Lymphogranuloma, bacteriology of lymphogranulomatosis and mycosis fungoides, 726
malignant lymphogranulomatosis and tuberculosis, 451
of spinal column, *
specific intracutaneous test for inguinal lymphogranulomatosis, 314
virus of inguinal lymphogranulomatosis, 451
Lymphosarcoma allergic skin phenomena in connection with generalized lymphosarcoma, 154
tracheal involvement in generalized lymphosarcomatosis, 458
Lysozyme and flocculation phenomenon of chicken egg-white, 730

McArthur, S. W.: Nasopharyngeal carcinoma, 879
McLaughlin, C. W.: Multilocular cystic lymphangioma of spleen, *655
McLennan, C. E.: Weights of various organs in adult rat after inanition with or without dietary accessories, 636
Macroglossia: See Tongue
Magnesium, does lack of magnesium affect transplantable tumors in rats, 585
Malaria, experimental studies on malaria of monkeys, 575
serologic studies in nonsyphilitic patients inoculated with tertian malaria, 730
Measles, colony formation of greening cocci from measles, 169
giant cells in tonsils in, 452
Mediastinum, tumors of thymic origin, 3 cases, 873
Medicine, legal, present status and future development in U. S., *542
Medicolegal journal, new, 567
Medium: See under names of bacteria, i. e., Tubercle Bacilli; etc.
Megakaryocytes, origin of megakaryocytes in extramedullary loci, 595
Melanoma, histology of, 585
studies, simple technique for Dopa reaction, 592
Meninges, cellular reactions in meninges of rabbits to tuberculo-lipoid, protein, and polysaccharide, compared with effects of tubercle bacilli, 447
diffuse meningeal carcinomatosis, 456
moniliasis with meningeal involvement, 600
Meningitis, experimental, cerebrospinal, 866
tuberculous, effect of allergy in, 299
Meningococcus, detoxification of meningococcus culture filtrates, 578
serological diversity among meningococci, 300
toxicity of various meningococcus preparations, 865
Meningo-Encephalitis: See also Encephalitis; Meningitis
Brucella meningo-encephalitis with mycotic aneurysm, 575
Mental diseases, is there a relation between blood group and mental diseases? 154
Mercuric chloride, shock syndrome in mercuric chloride poisoning, *509
Mercurosal: See Salyrgan
Mesaortitis: See Aortitis
Mesentery, xanthomatous transformation of, 290
Metabolism, respiratory metabolism and tissue respiration in experimental anaerobic infection, 137
Micrococcus pharyngis siccus endocarditis, 446
Microglia: See Neuroglia
Milk, poliomyelitis apparently due to a streptococcus in milk, 145
primitive or filtrable forms of bacteria and their occurrence in aseptic milk, 448
Milles, G.: Enterogenous cysts and diverticula, 172
Mohs, F. E.: Rat carcinoma and injected colloidal platinum, *796
Moniliasis with meningeal involvement, 600
Monocytes: See Leukocytes
Moon, V. H.: Shock syndrome in mercuric chloride poisoning, *509
Mosquitoes, transmission of neurotropic yellow fever virus by Stegomyia mosquitoes, 864
Mouth, core drill (trephine) for postmortem exposure of accessory nasal sinuses, nasal passages, mouth and pharynx, *255

Mucocele, unsuspected hemochromatosis with mucocele of appendix, 750
Müller's reaction; production of "ball" phenomenon in colloidal solutions of cholesterol and in cholesterolized lipoid mixtures by hydrochloric acid and sodium chloride, 732
Muir, K. B.: Methods for microchemical demonstration of arsenic in tissues, *789
Muscle respiration stimulated by carbon monoxide, 716
Mycobacteria: See under Bacteria
Mycosis fungoides, bacteriology of lymphogranulomatosis and mycosis fungoides, 726
Myelitis, Trinidad outbreak of acute rabic myelitis, 149
Myeloma, 307
in child, 736
solitary plasma cell myeloma, 749
Myocarditis perniciosa, 441
Myocardium, myocardial infarction or gross fibrosis, 143
Myositis, acute hemorrhagic myositis, 721
nonpurulent polymyositis, 292
Myxomatosis, infectious myxomatosis (Sanarelli) in pregnant rabbits, 578

Nasopharynx, carcinoma, 879
National Research Council, medical fellowship board of, 714
Nephritis: See under Kidney
Nerve Cells: See Neurons
fibers, silver impregnation of nerve fibers in paraffin sections, 592
influence of vestibular nerves and in particular nerves of Deiters on tendon reflexes, 434
silver impregnation of glia and nerve fibers in paraffin sections after formalin fixation, 593
Nervous System, chromaffin tumors of, 2 cases, 455
Neuroblastoma, relation to so-called adenosarcoma in kidney to neuroblastoma, 158
Neuro-epithelioma of lung, 590
Neurofibromas, multiple neurofibromas; case with 5 different types of tumors, 874
Neuroglia, silver impregnation of glia and nerve fibers in paraffin sections after formalin fixation, 593
staining of oligodendroglia and microglia in pyroxilin (celloidin) sections, 315
Neurons, intracranial inclusions in human nerve cells in a variety of diseases, 570
method for progressive selective staining of Nissl and nuclear substance in nerve cells, 313
Neurosyphilis: See under Syphilis
New-Born: See under Infant
Niemann-Pick disease, phosphatid content of brain in Niemann-Pick disease, 284
phosphatide degeneration of cells of brain, liver and spleen in Niemann-Pick's disease, 861
Nipple, changes in mammary gland produced by removal of nipple, 158
Nose, core drill (trephine) for postmortem exposure of accessory nasal sinuses, nasal passages, mouth and pharynx, *255
tumors of nasal cavity, 454
Nupercaine-Ciba, fatal medicinal poisoning by, 591
Nutrition, weights of various organs in adult rat after inanition with or without dietary accessories, *636

Obituaries:

Brebner, William B., 133
Ophüls, W., 885

Occipital puncture, new method for occipital puncture in rabbit, 161
O'Hare, J. P.: Experimental chronic nephritis produced by radium, *465
Olcott, C. T.: Contact carcinomas of stomach, 599
Oligodendroglia: See Neuroglia
Oliver, J.: Plastic studies in abnormal renal architecture; two architectural units in chronic Bright's disease and their possible functional significance, *755
Oncocytes, salivary gland tumors composed of oncocytes, 735
Orchitis: See under Testicle
Organ extracts, influencing anaphylactic symptoms and shock with organ extracts, 729
weights of various organs in adult rat after inanition with or without dietary accessories, *636
Osteitis deformans, 848
deformans, Paget's osteitis deformans, 854
fibrosa, 286
generalized fibrous osteitis associated with parathyroid tumor, 734
Osteodystrophy, experimental fibrous osteodystrophy in dog with pseudotumors and cysts of jaw, 568
Osteogenesis: See Bone, growth
Imperfecta: See Bone, fragility
Osteophytosis, cancer metastases in bone with special reference to osteophytosis, 155
Osteopoikilosis, disseminated condensation of bones, 288
Osteoporosis: See Bone, fragility
Osteosclerosis, myeloid leukemia with osteosclerosis, 602
Ostitis, fibrous, experimental osteoporosis and fibrous ostitis in dogs, 720
Otitis media, changes in middle and internal ear following chronic otitis media, 438
Ovary, granulosa cell tumor of ovary, 747
tumors of ovary with tissue like that of thyroid gland, 873
Ovum, implantation and structure of human ovum near seventeenth day (primitive streak stage), 879

Paget's Disease of Bone: See under Bone
Pancreas, accessory, persistent truncus arteriosus and congenital absence of one kidney with other developmental defects, *51
cancer; localization and metastasis of primary carcinoma of pancreas, 736
effect of ligation of pancreatic ducts on islands of Langerhans, 283
lipomatosis in child, 444
multiple hemangioblastomas of spinal cord with syringomyelia and cysts of pancreas and kidney (Lindau's disease), 604
Pancreatic ducts, effect of ligation of pancreatic ducts on islands of Langerhans, 283
Papilloma, case of multiple papillomata of larynx with aerial metastases to lungs, 585
Paralysis, jake paralysis following ingestion of Jamaica ginger extract adulterated with triortho-cresyl phosphate, 718
Parathyroids, congenital absence of, 722
tumor, generalized fibrous osteitis associated with parathyroid tumor, 734
Paratyphoid, agglutinin-formation after oral immunization against typhoid and paratyphoid fever, 867
agglutinin responses to typhoid-paratyphoid vaccination, 301
and typhoid infections in rabbits, 296
B, effect of bacteriophage on Forssman and human blood antigens in B. paratyphoid B and in B. dysenteriae Shiga, 303
Parker, R. R.: Certain phases of problem of Rocky Mountain spotted fever, summary of present information, *398
Parotid, changes in epithelium of explanted parotid gland, 850
Parrots, a virus disease of parrots and parrakeets differing from psittacosis, 446
Pasternack, J. G.: Metastasizing chondrosarcoma of coronoid process of mandible, *649
Pasteurella: See Bacteria, Pasteurella
Pathology, disease among Chinese and geographic pathology, 436

Peptic ulcers and interbrain, 433
Periarteritis nodosa, borderline cases, 291
nodosa; necrotizing arteritis and subacute glomerulonephritis in gonococcic endocarditis; toxic origin of periarteritis nodosa, *35
Pericardium, primary carcinoma, 873
Periosteum, effect of viosterol on periosteum and experimental fracture, 718
Peritoneum, diffuse carcinomatosis of peritoneum, 155
primary round-celled sarcoma of peritoneum, 305
pseudomyxoma of peritoneum of appendical origin, 735
Pharynx, core drill (trephine) for postmortem exposure of accessory nasal sinuses, nasal passages, mouth and pharynx, *255
Pheochromocytoma, a suprarenalin-producing pheochromocytoma of suprarenal gland, report of case, *665
Phosphates, simple quantitative microcrystallographic estimation of phosphates in urine, *213
Phosphorus, organic phosphorus compounds and phosphatase in mammary gland, 862
poisoning, 738
poisoning, central nervous system in, 144
Pineal body, tumor of, 733
Pituitary Body, actinomycosis of hypophysis cerebri and actinomycotic leptomeningitis, 725
diabetes insipidus in a patient with tumor metastasis to hypophysis, 134
gumma of hypophysis and hypothalamus, *631
relation of abnormalities of body of sphenoid bone to adiposogenital syndrome, 855
Pituitary Extract, comparison of hypertrophic changes in thyroid caused in different species by acid extract of anterior lobe of bovine pituitary gland, *67
effect of pituitary anterior lobe hormone on testis, 435
Plasmocytoma, solitary, 588
Platinum, rat carcinoma and injected colloidal platinum, *796
Pleura, effusion, tubercle bacilli in, 295
Pneumococcus, antipneumococcus properties of normal swine serum, 151
antipneumococcic reactions by human beings, 150
antipneumococcic reactions of rabbits, 151
carriers, specific therapy of, 153
presence in antipneumococcic serum of nonantibacterial therapeutic factor, 300
quantitative action of specific enzyme in type III pneumococcus dermal infection in rabbits, 299
therapeutic value of type I pneumococcus antiserum, 152
virulence of, 447
Pneumoconiosis and tuberculosis, 453
clumps of asbestosis bodies in sputum of asbestos workers, 853
Pneumonia, epidemic of croupous pneumonia caused by pneumococcus, type I, 146
from aspiration of fat and oil in lungs, 288
in children, 580
pathogenesis of experimental pneumococcic lobar pneumonia in dog, 878
specific histology of interstitial pneumonia of acquired syphilis, 723
spread of inflammatory process within lung in lobar pneumonia, 856
Poisoning: See also under names of specific substances
cooperation of physician and chemist in detection of fatal poisoning, 738
Poliomyelitis, 595
apparently due to a streptococcus in milk, 145
attempt to transmit poliomyelitis to splenectomized guinea-pigs, *387
blood grouping in, 300
Poliomyelitis—Continued
chronic, syphilitic, 143
experimental, nerve degeneration in physiologic and histologic studies on roots and nerves supplying paralyzed extremities of monkeys during acute poliomyelitis, 143
immunization against, 299
neutralizing effect of pooled human serum on poliomyelitis virus, 582
passage of poliomyelitis virus through intestinal tract, 148
purification and concentration of virus of poliomyelitis, 577
purification of poliomyelitic virus, *221
toxic substance in feces and urine in, 582
virus in so-called abortive types of disease, 577
Polyarthritis: See Arthritis
Polymyositis: See Myositis
Polypoid tumors of left auricle of heart, 872
Poncher, H. O.: Enterogenous cysts and diverticula, 172
Portal vein, experimental sclerosis of, 435
Postmortem: See Autopsies
Potter, J. S.: Mouse leukemia; continuity of cell lineage in transmission lines of lymphatic leukemia, *198
Precipitin; serological reactions with simple chemical compounds (precipitin reactions), 728
Pregnancy, function of fetal spleen in splenectomized pregnant rats, 285
lipoid antigens and antibodies in malignancy and pregnancy, 302
test, Friedman modification of Aschheim-Zondek pregnancy test, 160
time at which casein begins to be formed in breast during pregnancy, 168
Pribram, E. A.: Simple quantitative microcrystallographic estimation of phosphates in urine, *213
Prize, Nordhoff-Jung cancer prize, 279
Prostate, hypertrophy, intersexuality and sexual relationships of prostate, 281
Protein, experimental edema from plasma protein depletion, 717
immunological behaviour of second protein (livetin) of hen's egg yolk, 299
Prothrombin, effect of prothrombin and heparin on proliferation and differentiation of tissues in vitro, 851
Pseudomyxoma of peritoneum of appendical origin, 735
Pseudotuberculosis, human pseudotuberculosis associated with hemochromatosis, 2 cases, 725
pseudotuberculous necroses of human liver, 445
Psittacosis, a virus disease of parrots and parrakeets differing from psittacosis, 446
with results of postmortem examination in a case including studies of spinal cord, 576
Pyridine-soda method for impregnation of mesoglia and reticuloendothelial cells, 314

Rabies, Trinidad outbreak of acute rabic myelitis, 149
Radiation: See Radium; Roentgen Ray; Ultraviolet Rays
Radium, comparison of biologic effects of beta rays of radium and roentgen-rays, 859
effect of radium emanation of histiocyte in liver of white rat, 287
experimental chronic nephritis produced by radium, *465
fatal fibrosis of lungs due to inhalation of radium, 571
water, poisoning from drinking radium water, 737
Radwin, L. S.: Effect of cinchophen on albinic rat, *490
Reflexes, influence of vestibular nerves and in particular nerves of Deiters on tendon reflexes, 434

Reimann, S. P.: Aberrant growths in regenerating claws of hermit crab under influence of sulphydryl; their relation to neoplasia, *675
Roentgenograms of breast and its lesions and their histologic correlation, 163
Relapsing fever, rôle of temperature in treatment of replapsing fever with arsphenamine, 285
Respiratory tract, changes in mucous membrane of upper respiratory tract in death by burning, 460
Reticulo-endotheliosis, aleukemic, with lipoid storage, case of, 443
case of, 442
chronic leukemic reticulo-endotheliosis, 724
extirpation of spleen and blockade of reticulo-endothelial system and its influence on tuberculosis, 298
infectious reticulo-endothelial hyperplasia in a child, 442
Reticulum fibers, significance of reticulum fibers in pulmonary tuberculosis, 571
in tumors, *498
Retina, angiomatosis of retina (von Hippel and Lindau's disease) 440
Rhabdomyoblastoma, 456
Rhabdomyoma, 734
Rhea, D.: Core drill (trephine) for postmortem exposure of accessory nasal sinuses, nasal passages, mouth and pharynx, *255
Rheumatic Fever, antihaemolysine titres in haemolytic streptococcal infections and their significance in rheumatic fever, 582
dissociation of streptococcus cardio-arthritidis, 147
relationship of streptococcus hemolyticus to rheumatic process, 863
search for streptococci in early lesions of acute rheumatice infection, 726
vascular involvement in, 438
Rheumatism, incidence and distribution of age of death in rheumatic heart disease, 715
relation of chronic polyarthritis to acute rheumatic infection, 282
spontaneous infectious rheumatism in mice, 866
suspected poisoning; death from rheumatic aortitis, 311
Richter, M. N.: Mouse leukemia; continuity of cell lineage in transmission lines of lymphatic leukemia, *198
Robertson, O. H.: Pathogenesis of experimental pneumococcic lobar pneumonia in dog, 878
Robertson, S. H.: Lipoid histiocytosis; report of case with diagnosis by biopsy, *193
Rocky Mountain spotted fever, certain phases of problem of, summary of present information, *398
pathologic anatomy of eastern type of, 852
rickettsiae, 448
Rodents, injuries to bones of human cadavers by rodents, 158
Roentgen Rays, comparison of biologic effects of beta rays of radium and roentgen-rays, 859
effect of roentgen irradiation on kidney, 568
experimental liver disease produced by X-ray irradiation of exposed organ, 848
maturing effect of roentgen rays on blood-forming cells, 717
Roome, N. W.: Traumatic shock syndrome following rupture of aorta and multiple fractures, 880
Rosbash, D. O.: Copper and "active" iron content of tissues, 171
Rosebury, T.: Problem of dental caries, *260
Rosenthal, M.: Anatomic lesions of fatal mercurial intoxication from salyrgan, *352
Ross, P. W.: Potentiometric determinations of malignant human and transplanted rat tumors, 169
Rye, influence of rye and of wheat bread on rats and mice, 726
Salivary Glands, histogenesis of mixed tumors of, 455
tumors composed of oncocytes, 735
unusual situation of tumors of mixed type, 733
Salyrgan, anatomic lesions of fatal mercurial intoxication from salyrgan, *352
Sano, M. E.: Moniliasis with meningeal involvement, 600
Sarcoma, causal relation of trauma to sarcoma of bone, 158
experimental bone sarcoma, 881
eye, 455
fibril-producing power of sarcomas, 157
of rat from external agencies, 155
primary round-celled sarcoma of peritoneum, 305
production of experimental sarcoma in rat, 155
tongue, 157
Scarlet fever, growth of erysipelas and scarlet fever streptococci on hemoglobin chocolate agar, 148
renal changes in mixed diphtheritic and scarlatinal infection, 855
Schaeffer, M.: Purification of poliomyelitic virus, *221
Schelm, G. W.: Chorion epithelioma of testicle with metastases, gynecomastia and pregnancy reaction (Friedman), 316
Schick, Béla Schick awarded Phi Lambda Kappa Medal, 132
Schilder's Disease: See Encephalitis periaxialis
Schüller-Christian syndrome, 443
Schultz, O. T.: Present status and future development of legal medicine in United States, *542
Schwannoma, experimental and spontaneous schwannoma (peripheral glioma), 586
Sclerosis, experimental sclerosis of portal vein, 435
small foci of demyelinization in diffuse sclerosis, 143
Scurvy, changes in teeth and jaws in experimental scurvy, 851
chemical and physicial properties of bone in experimental scurvy, 860
Seabold, P. S.: Roentgenograms of breast and its lesions and their histologic correlation, 163
Secretin, 848
Seelig, M. G.: Reticulum in tumors, *498
Serous cavities, primary malignant tumors of, 458
Serum, bactericidal power of normal serum, 582
effect of light on bactericidal properties of serum, 733
immunologic properties of normal serum, 304
removal of anaphylactogenic properties of serum, 730
Sickness: See Anaphylaxis and Allergy
Sex, method for prediction of sex in unborn, 719
Shock, death from shock during boxing match, 877
syndrome in mercuric chloride poisoning, *509
traumatic shock syndrome following rupture of aorta and multiple fractures, 880
Shute, E.: Histologic changes in rabbits and in dogs following intravenous injection of thorium preparations, *27
Silicosis: See Pneumoconiosis
Silver; argyria with gigantic stone in bladder, 751
Skeletal remains, identification of, 460
Skin, comparative histologic reactions in cutaneous lesions induced by streptococci in rabbits previously inoculated intracutaneously or intravenously, *611
variations in distribution of elastic fibers in human skin, 573

Smetana, H.: Coccidiosis of liver in rabbits; experimental study of histogenesis of coccidiosis of liver, *516
Coccidiosis of liver in rabbits; experimental study on excystation of oocysts of Eimeria stiedae, *175
Coccidiosis of liver in rabbits; experimental study on mode of infection of liver by sporozoites of Eimeria stiedae, *330
Smith, G. V. S.: Primary epithelial tumors of vermiform appendix; observations by silver impregnation, *78
Smith, L. W.: Moniliasis with meningeal involvement, 600
Soap necrosis of pregnant uterus, 591

Society Transactions:
Chicago Pathological Society, 164, 315, 878
New York Pathological Society, 599
New York Pathological Society and New York Academy of Medicine, Section of Surgery, 741
Pathological Society of Eastern New York, 747
Pathological Society of Philadelphia, 162, 594, 876

Specimens, new embedding material, 160
Spermatogenesis, effect of ligation of efferent seminal path on spermatogenesis, 437
Sphenoid, relation of abnormalities of body of sphenoid bone to adiposogenital syndrome, 855
Spinal Cord, multiple hemangioblastomas of spinal cord with syringomyelia and cysts of pancreas and kidney (Lindau's disease), 604
psittacosis with results of postmortem examination in a case including studies of spinal cord, 576
Spine, changes in vertebral column in acromegaly, 292
lymphogranulomatosis of spinal column, 574
skeletal conditions in craniorachischisis, 571
Spirochaeta pallida, thermal death time of Treponema pallidum in vitro, 863
Spirochetes, distribution of spirochetes of type Weil in Freiburg-i.-Br. and vicinity, 727
spontaneous spirochetosis and experimental syphilis in rabbits, 575
Spleen, accessory, persistent truncus arteriosus and congenital absence of one kidney with other developmental defects, *51
experimental production of areas of sidero-fibrosis in, 282
function of fetal spleen in splenectomized pregnant rats, 285
function of spleen in Bartonella infection of white rat, 731
lymphoblastoma of spleen with splenectomy, 748
multiocular cystic lymphangioma of spleen, *655
phosphatide degeneration of cells of brain, liver and spleen in Niemann-Pick's disease, 861
rôle of leukocytolysines of spleen in anaphylactic shock, 728
rôle of spleen in iron metabolism, 720
spontaneous subcapsular rupture of spleen, 292
structural changes in spleen of rats in streptococcal infection, 149
thickening of pulmonary apex and splenic capsule, 291
Splenectomy, attempt to transmit poliomyelitis to splenectomized guinea-pigs, *387
changes produced in blood picture by, 431
effect of experimental splenectomy on blood platelets and bone marrow, 284
Sporotrichosis, transmission to plants and animals, 146
Sputum, clumps of asbestos bodies in sputum of asbestos workers, 853
Stahr, G. E.: Chorion epithelioma of testicle with metastases, gynecomastia and pregnancy reaction (Friedman), 316
Stains and Staining; method for progressive selective staining of Nissl and nuclear substance in nerve cells, 313
new rapid staining of tubercle bacilli in sputum, 161
of insoluable calcium salts in tissues, 740
of intracellular fat in tissue culture, 740
of oligodendroglia and microglia in pyroxilin (celloidin) section, 315
Staphylococcus aureus; dissociation and its relation to infection and to immunity, 580
formol detoxication of purified staphylococcal toxin, 451
growth requirement of, 293
heat inactivation of antistaphylococcus bacteriophage, 580
Status Lymphaticus: See Lymphatism
Steam inhalation, death from, 875
Steatorrhea, idiopathic steatorrhoea (Gee's disease), 849
Stillbirths, causes of death in stillbirths, 140
microscopic cerebral hemorrhage in stillbirths and newborn deaths, 286
Stomach, cancer, comparative statistical study, 156
cancer; contact carcinomas of stomach, 599
cancer; "disseminated carcinoma" of stomach, 459
injuries of stomach and duodenum by blunt violence, 310
syphilitic plastic linitis, 721
tumors, multiple, 589
ulcer in albino rats deprived of vitamin B (B_1), 432
Strangulation, manual, *55
Streptococcus, acute glomerulitis following injection of streptococcus viridans into renal artery, 718
and diphtheroid bacillus in acute endocarditis, 574
antihaemolysine titres in haemolytic streptococcal infections and their significance in rheumatic fever, 582
cardioarthritidis, dissociation of, 147
comparative histologic reactions in cutaneous lesions induced by streptococci in rabbits previously inoculated intracutaneously or intravenously, *611
growth of erysipelas and scarlet fever streptococci on hemoglobin chocolate agar, 148
hemolytic streptococci; their grouping by agglutination, 583
infection, structural changes in spleen of rats in streptococcal infection, 149
production of specific bacteriotropins in infections with haemolytic streptococci, 583
relationship of streptococcus hemolyticus to rheumatic process, 863
search for streptococci in early lesions of acute rheumatic infection, 726
variations in resistance to infections with streptococci following immunization with heterobacteria, 729
viridans, biology of, in endocarditis lenta, 297
Sulphydryl, aberrant growths in regenerating claws of hermit crab under influence of sulphydryl; their relation to neoplasia, *675
Suprarenal Preparation; extract of suprarenals of horse as antigen for Wassermann reaction, 732
Suprarenals, combined disease of suprarenal and thyroid glands, 135
pathologic anatomy and abnormal physiology of, 136
relation of suprarenals to hypertension and arteriosclerosis, 436
suprarenalin-producing pheochromocytoma of suprarenal gland, report of case, *665
transplantation of adrenal cortical tissue in rat, 716

Suprarenals—Continued
tumors of cortex; 3 cases of cancer and 1 lipoma, 881
tumors of suprarenal gland, *775
Sutro, C. J.: Fluorescence of cartilage exposed to filtered ultraviolet radiation, *537
Sweany, H. C.: A live steam inspissator attachment for autoclave, *539
Swift, H. F.: Comparative histologic reactions in cutaneous lesions induced by streptococci in rabbits previously inoculated intracutaneously or intravenously, *611
Syphilis, chemical nature of so-called syphilis antigens, 732
chronic syphilitic poliomyelitis, 143
diastase content of spinal fluid, 739
employment of pallida antigens for serodiagnosis of syphilis, 870
enlargement of aortic valve in syphilitic aortitis, 572
healing of experimental syphilis in rabbits by short wave fever, 864
microscopic slide precipitation test for syphilis with spinal fluid, 160
Müller test for syphilis, 309
nonspecific orchitis and keratitis in experimental syphilis, 147
peculiar form of nephritis associated with acquired syphilis, 289
positive seroreactions for syphilis following injection of antidiphtheria serum, 585
relations between syphilitic aortitis and atherosclerosis, 573
specific histology of interstitial pneumonia of acquired syphilis, 723
spontaneous spirochetosis and experimental syphilis in rabbits, 575
syphilitic plastic linitis, 721
Wassermann reaction and certain precipitation reactions, 593
Syringomelia, multiple hemangioblastomas of spinal cord with syringomyelia and cysts of pancreas and kidney (Lindau's disease), 604
pathogenesis and morphology of syringomyelia, 572

Takayama's solution in identification of blood stains, 161
Tannenholz, H.: Methods for microchemical demonstration of arsenic in tissues, *789
Teeth, caries, *260
changes in teeth and jaws in experimental scurvy, 851
structure of teeth in cases of extensive skeletal changes, 572
Teratoma, retroperitoneal, 454
Terrell, E. E.: Pathogenesis of experimental pneumococcic lobar pneumonia in dog, 878
Testis, chorionepithelioma of, 589
chorionepithelioma of testis with abnormal development of male breast, 307
chorionepithelioma of testicle with metastases, gynecomastia and pregnancy reaction (Friedman), 316
coincident carcinoma and tuberculosis of testis, 457
effect of high external temperature on testis, 436
effect of pituitary anterior lobe hormone on testis, 435
nonspecific orchitis and keratitis in experimental syphilis, 147
structure of 2 testicular grafts after survival of 6 years, 849
Thorium dioxide, experimental hepatitis and cirrhosis produced by thorium dioxide, 850
histologic changes in rabbits and in dogs following intravenous injection of thorium preparations, *27
Thrombophlebitis, cervical thrombophlebitis and sepsis secondary to tonsillar infection, 439
Thrombozytobarine, significance of thrombozytobarine as a defensive mechanism in infection, 728
Thurston, E. W.: Comparison of hypertrophic changes in thyroid caused in different species by acid extract of anterior lobe of bovine pituitary gland, *67
Thymus, mediastinal tumors of thymic origin, 3 cases, 873
Thyroid, combined disease of suprarenal and thyroid glands, 135
comparison of hypertrophic changes in thyroid caused in different species by acid extract of anterior lobe of bovine pituitary gland, *67
effect of partial resection on thyroid, 135
experimental epithelial metaplasia of, 280
histologic changes in rabbit following injection of urine, *321
hyperthyroidism; absence of osteoporosis demonstrated chemically in clinical hyperthroidism, 431
malignant tumors of, 743
osseous tumors with thyroid structure, 306
tissue reaction to colloid and lipoids from, *244
tumor of ovary with tissue like that of thyroid, 873
tumors, pathologic aspects, 741
Tissue cultures; growth of tissue cultures in immune serum, 851
demonstration of elements in tissues; gold and silver, 314
effect of prothrombin and heparin on proliferation and differentiation of tissues in vitro, 851
specificity of tissue and blood reaction, 289
Tongue, aglossia congenita, 141
localized amyloidosis with macroglossia, 723
sarcoma of, 157
Tonsils, Brucella abortus in tonsils, 576
cervical thrombophlebitis and sepsis secondary to tonsil infection, 439
function, 138
giant cells in tonsils in measles, 452
Trachea, mucus secretion in, 289
tracheal involvement in generalized lymphosarcomatosis, 458
Treponema Pallida: See Spirochaeta pallida
Trichomonas hominis, invasion of wall of intestine by Trichomonas hominis, 446
Trio-ortho-cresyl phosphate, jake paralysis following ingestion of Jamaica ginger extract adulterated with tri-ortho-cresyl phosphate, 718
Trubek, M.: Necrotizing arteritis and subacute glomerulonephritis in gonococcic endocardtis; toxic origin of periarteritis nodosa, *35
Tubercle Bacilli, action of radium rays on tubercle bacilli in culture, 296
bovine, variability of, 454
C-form of, 454
cellular reactions in meninges of rabbits to tuberculo-lipoid, protein, and polysaccharide, compared with effects of tubercle bacilli, 447
conditions for isolation of tubercle bacilli from blood, 739
cultivation from blood by Löwenstein's method, 740
do tuberculous and nontuberculous serums possess bactericidal properties for tuberculosis bacillus? 729
effect of human blood serum on human tubercle bacilli, 870
estimation of number of organisms in suspensions of tubercle bacilli, 739
filtrability of pure cultures of tubercle group of micro-organisms, 450
in blood stream of rabbits during course of infection, 294
in hen's eggs, 298

Tubercle Bacilli—Continued
in urine as manifestation of systemic infection in pulmonary tuberculosis, 298
isolation and differentiation of tubercle bacilli on Bordet-Gengou and Löwenstein mediums, 865
isolation of tubercle bacilli from blood according to Löwenstein, 298
isolation of tubercle bacilli from pleural effusions, 295
microchemical studies of nonacid-fast tubercle bacilli, 295
morphologic variability of tubercle bacillus (human type) in cultures, 295
new rapid staining of tubercle bacilli in sputum, 161
tissue substrate microculture for tubercle bacilli, 739
virulence of, 453
Tuberculin sensitiveness following infection with tuberculosis bacilli of varying virulence, 729
Tuberculosis: See also under names of organs and regions
argentophile fibers in miliary tuberculosis, 853
B C G: increase in virulence of Calmette bacillus, 295
bovine; diphasic nature of bovine tuberculosis in rabbits, 448
diagnostic value of blood culture in experimental tuberculosis of rabbit, 453
do tuberculous and nontuberculous serums possess bactericidal properties for tuberculosis bacillus, 729
effect of lymphocytosis from chick embryo extract on tuberculosis in rabbits, 448
experimental tuberculous infection in tissue culture, 452
extirpation of spleen and blockade of reticuloendothelial system and its influence on tuberculosis, 298
human tuberculosis in rabbits, 866
immunity and complement fixation, 871
immunological studies, 153
inflammatory reaction in, 598
interstitial reactions caused by various dusts and their influence on tuberculous infections, 150
malignant lymphogranulomatosis and tuberculosis, 451
metabolism of tuberculous patients and influence of nutrition, 851
of systemic arteries with fatal rupture, 852
pneumoconiosis and tuberculosis, 453
primary intestinal tuberculous complex, 296
pulmonary, cavernous pulmonary phthisis without involvement of apexes, 296
pulmonary, etiologic diagnosis in childhood, 296
pulmonary, significance of reticulum fibers in, 571
pulmonary, tubercle bacilluria as manifestation of systemic infection in pulmonary tuberculosis, 298
pulmonary, water metabolism in, 851
tuberculin sensitiveness following infection with tuberculosis bacilli of varying virulence, 729
Tularemia, diagnosis by means of intradermal reaction, 581
induction of avirulence in Pasteurella tularensis, 581
immunologic studies on tularemia in rabbits, 581
Tumors: See also Cancer; and under names of organs and regions
aberrant growths in regenerating claws of hermit crab under influence of sulphydryl; their relation to neoplasia, *675
diagnosis by puncture, 308
does lack of magnesium affect transplantable tumors in rats? 585
Tumors—Continued
effect of carbon monoxide and other agents upon rate of tumour growth, 305
follicular hormone content of blood of male tumor-bearing mice, 156
granulosa cell tumor of ovary, 747
histologic diagnosis of tumors by means of histochemical demonstration of cholesterol, 155
immunity, 305
implantation and contact metastases of malignant tumor, 873
potentiometric determinations of malignant human and transplanted rat tumors, 169
reducing power of certain tumors, 587
properties of causative agent of a chicken tumor, 587
reticulum in, *498
structure of malignant tumor cell, 734
successful isolation of Rous tumor agent by means of capillarity, 308
transmission of fowl-tumours to pheasants, 305
Tunnicliff, R.: Colony formation of greening cocci from measles, 169
Tureen, L. L.: Blood diastase in cancer, *834
Reticulum in tumors, *498
Typhoid, agglutinin formation after oral immunization against typhoid and paratyphoid fever, 867
agglutinin responses to typhoid-paratyphoid vaccination, 301
and paratyphoid infections in rabbits, 296
experimental infection of mice with typhoid bacilli, 727
isolation of motile organisms from apparently non-motile cultures of B. typhosus, etc., 149
organism intermediate between Bacillus typhosus and Bacillus dysenteriae Shiga from atypical typhoid, 146
vaccine, effect of intracutaneous injections of typhoid vaccine in typhoid, 304
Typhus Fever, different varieties of typhus fever and their biologic differentiation, 297
endemic, of United States, 451
experimental transmission of endemic typhus fever of United States by rat flea (Xenopsylla cheopis), 294
rickettsiae, 447

Ulcers: See Peptic Ulcer; and under names of organs
Ultrafilters, preparation of a graded series of ultrafilters and measurement of their pore sizes, 160
Ultraviolet radiation, fluorescence of cartilage exposed to filtered ultraviolet radiation, *537
Urine, histologic changes in thyroid of rabbit following injection of urine, *321
simple quantitative microcrystallographic estimation of phosphates in urine, *213
tubercle bacilluria as manifestation of systemic infection in pulmonary tuberculosis, 298
Urticaria, passive transference of urticarial hypersensitiveness to fungus extracts, 301
Uterus, soap necrosis of pregnant uterus, 591

Vaccination, Encephalitis following: See under Encephalitis
Vaccine virus, cultivation of vaccine virus in lifeless media, 865
Vaccinia, vaccinial infection of chorio-allantoric membrane of chick embryo, 446
Varix, pulmonary varix with spontaneous rupture and death, report of case, *227
Veronal: See Barbital
Vertebra: See Spine
Vibrios from intestinal tract of gray rat, 446
Viosterol: See Ergosterol
Viruses, preparation of graded series of ultrafilters and measurement of their pore sizes, 160

Vitamin B (B_1), gastric ulcer in albino rats deprived of vitamin B (B_1), 432
D, effect of vitamin D on bone, 435
E deficiency, 134
E, effect of deficiency of vitamin E on female rat, 137
Vocal cords, carcinoma of, 458

Walsh, E. L.: Etiology of gallstones, *698
Warren, S.: Lipoid histiocystosis; report of case with diagnosis by biopsy, *193
Wartman, W. B.: Incidence and severity of arteriosclerosis in 500 autopsies, 876
Wassermann reaction and certain precipitation reactions, 593
aspecific, 871
extract of suprarenals of horse as antigen for Wassermann reaction, 732
serologic studies in nonsyphilitic patients inoculated with tertian malaria, 730
Water in lungs of drowned animals, *828
metabolism in pulmonary tuberculosis, 851
Weather, influence of changes in weather on approaching death, 280
Weights of various organs in adult rat after inanition with or without dietary accessories, *636
Weil, A.: Staining of oligodendroglia and microglia in pyroxilin (celloidin) sections, 315
Weiss coagulo-flocculation test of malignancy, *393
Wheat, influence of rye and of wheat bread on rats and mice, 726
Wilens, S. L.: Multiple hemangioblastomas of spinal cord with syringomyelia and cysts of pancreas and kidney, 604
Winkelman, N. W.: Poliomyelitis, 595
Wolf, A.: Multiple hemangioblastomas of spinal cord with syringomyelia and cysts of pancreas and kidney (Lindau's disease), 604
Wright, A. W.: Solitary plasma cell myeloma, 749

Xanthogranulomatosis (so-called Schüller-Christian disease), 443
Xanthoma, xanthomatous transformation of mesentery, 290

Yellow fever, immunity tests in, 298
transmission of neurotropic yellow fever virus by Stegomyia mosquitoes, 864
vaccination with immune serum and virus fixed for mice, 152

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PAGE

...ICTURE: I. THE
...RIGHT'S DISEASE
...FICANCE. JEAN
...ROOKLYN..... 755

...Z. GESCHICKTER,
..... 775

...OF ARSENIC IN
...H KATHLEEN P.
..... 788

...TINUM. M. F.
..... 795

...S IN THE GALL-
...TUDIES ON CATS
...ND EMMANUEL
..... 818

...ALS. PETER V.
..... 828

...TUBEEN, M.D.,
..... 834

...LOBIN BY CELL
..., NEW YORK.. 840

..... 847

..... 848

..... 876

..... 878

..... 883

..... 885

..... 887